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EDITED BY N. RASHEVSKY
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A NEURAL MECHANISM FOR DISCRIMINATION: II. DISCRIMINATION OF WEIGHTS

A. S. HOUSEHOLDER
The University of Chicago

A theoretical central mechanism for the discrimination of intensities as previously developed, together with plausible assumptions concerning the receptors, are employed for the derivation of the discriminable difference between lifted weights as a function of the smaller of these weights. The function so derived depends upon three parameters, one parameter being the weight of the supporting member. Some empirical data are compared with the theoretical predictions, and a few remarks are added to describe the physiological significance of the parameters.

1. *Some suggested central mechanisms for discrimination.* In continuation of a previous discussion (Householder, 1939; this paper will be denoted hereafter by the letter D.) we consider a hypothetical neural mechanism, whose elements have properties suggested by actual nerve fibers, and which has itself the property of diverting excitations of different intensities along different sets of paths. Our object will be to derive a formula for the just-noticeable difference in stimulus intensity for the particular sense of tension, and to compare this with some existing experimental data.

For the most part, theorizing on the subject of discrimination of stimulus intensities is restricted, implicitly or explicitly, to the psychological level. Most satisfying of the purely psychological theorizing in this direction are the psychophysical papers of L. L. Thurstone (1927, to cite only one), where the restriction is explicitly imposed and the argument unentangled by neurological concepts irrelevant to the problems and methods which he discusses.

On the neurological level, E. D. Adrian (1932) notes the approximately logarithmic relation between intensity of stimulation and frequency of response of a single receptor, an interesting point in connection with Fechner's law. But evidently, on the one hand, a set of logarithmically responding receptors will not necessarily respond logarithmically as a set, and on the other hand, even if they do so the nature of the discriminal process is still unsettled.

A. H. Holway and C. C. Pratt (1936) note the qualitative similarity between the curves for several modalities obtained by plotting the Weber-ratio against the stimulus intensity, and A. H. Holway and L. M. Hurvich (1937) conclude that "Differential sensitivity can be regarded as a direct measure of the number of elements (= number of impulses per unit time) available for the discrimination of a minimal change in the intensity of stimulation." In their discussion, Holway and Hurvich employ neurological terms chiefly to show the consistency of this notion with current neurological principles. No neural mechanism is described, however, to show how the available elements could be so organized that a lesser stimulus might traverse paths not reached by a stronger one. Oberlin's (1934) suggestion that thresholds of the receptor elements have a nearly normal distribution also falls short in this respect. Such an assumption, however, is to be included among those employed in the present paper (*vide infra*).

H. Piéron (1933) makes a suggestion somewhat as follows. If two antagonistic effectors are reached by paths from the same centers with one having a higher threshold than the other, and if the one with higher threshold exerts some kind of an inhibiting effect upon the other, then indeed we should have a mechanism whereby quantitatively different stimulus intensities might lead to qualitatively different responses. Evidently the crucial features of this mechanism are the difference in thresholds at two synapses (or sets of synapses) and the inhibition exerted by one of these (sets of) synapses upon the other. Whether these elements be placed at the effectors themselves or at some intermediate station is of no importance theoretically. In a sense the mechanism here to be discussed is an elaboration of the one suggested by Piéron.

N. Rashevsky (1938 a) and H. D. Landahl (1938) consider systems of neurons having the property that if two receptors (two sense organs or two parts of the same sense organ; e.g. two areas of the retina), O_1 and O_2, are stimulated with unequal intensities S_1 and S_2, and if stimulation of O_1 alone would lead to response R_1, and stimulation of O_2 alone would lead to response R_2, then the simultaneous stimulations will lead to R_1 or R_2 alone according as S_1 exceeds or is exceeded by S_2. If E_1 and E_2 are the two effectors, it is only necessary to connect O_1 to E_2 and also O_2 to E_1 by inhibitory neurons. With suitable quantitative relations the intensity of the response will depend upon the ratio S_1/S_2 alone, and not upon the absolute magnitudes of these intensities (Rashevsky, 1938 a, ch. xxvi). Landahl considers the same mechanism with the added assumption that either or both excitatory paths is subject to a random fluctuation. In a recently published paper Landahl (1940) has shown further that by introducing suitable neuron circuits (Rashevsky, 1938 a, ch. xxiv) it is possible to delay the reaction to the first stimulus and to eliminate the requirement of simultaneous presentation of the two stimuli. Hence, knowing the distribution of the random fluctuations one may calculate the distribution of the judgments. If we call one of the stimuli the "standard", presumably there will be a distribution curve for each standard, and with a suitable definition of a "noticeable" difference the Weber-ratio is defined for this particular standard.

Another possible mechanism has been described by Landahl (1939), this one consisting of a set of neurons capable of transmitting excitations only if the stimulus lies in a limited intensity range. This consists of three neurons: an excitatory one and an inhibitory one, having the same threshold and leading from the same initial synapse, and both synapsing with the third neuron. The lower limit of the intensity-range is the common threshold of this initial neuron-pair; the upper limit depends upon the parameters of their excitation equations, and upon the threshold of the efferent neuron. Given a system of such neuron-triples with varying ranges, a stimulus S will act upon only those effectors reached by those triples whose range contains S. If, for example, we define two stimuli, S_1 and S_2, as "completely discriminable" in case no neuron-triple of this system exists whose range includes both S_1 and S_2, then one could calculate the distribution of the ranges within the system from the empirical function defining, for the modality in question, the Weber-ratio in terms of the stimulus-intensity.

The third mechanism, on which the ensuing discussion is based, is due, in its essential features, to Rashevsky (1938 b), and was developed in greater detail in the paper D. Instead of accompanying each first-order excitatory neuron by a parallel inhibitory neuron, the inhibitory neurons interconnect the terminal synapses. Since the amount of inhibitory substance, j, developed by the inhibitory neurons, depends upon the excess of ε over j at these terminal synapses, and since this excess itself depends upon j, we are led to an integral equation for the determination of $\varepsilon - j$ at each of the terminal synapses. If the primary neurons vary as to threshold it turns out, as with Landahl's mechanism described above, that when any intensity S is applied to all the initial synapses, ε exceeds j at only a limited number of the terminal synapses. If two stimuli, S_1 and S_2, are defined to be "completely discriminable" when the sets of terminal synapses at which ε exceeds j are distinct for these stimuli, then we can deduce the Weber-function defining the Weber-ratio in terms of the stimulus intensity.

To avoid a possible misunderstanding, let it be said that the definition of "completely discriminable" stimuli is not to be taken as implying that complete discriminability exists psychologically. Indeed, even at the neurological level J. Erlanger and H. S. Gasser (1937) find unpredictable fluctuations in the thresholds of individual neurons. It is enough to assume that stimuli which are just completely discriminable in our sense will be experimentally discriminated in a suitable percentage (say 75%) of the trials.

Strictly speaking, another parameter should enter here into our Weber-function. Empirically a Weber-function could be obtained for each choice of the percentage required, and hence a one-parameter family of functions is empirically obtainable. It is assumed that one of these functions should agree with the function theoretically deduced, but unless an additional assumption is made which will enable us to predict which one it is (i.e. just what percentage corresponds to complete discriminability), this can only be decided experimentally. Actually we no not make this assumption, nor do we find experimental results sufficiently stable to allow the calculation of the family of curves with any reasonable accuracy. Hence in comparing theory with experiment we assume that the experimenter's choice of the percentage is correct within the limit of experimental error.

2. *Receptors and first-order neurons.* We have spoken above of primary, or first-order neurons, initial and terminal synapses, and stimulus-intensities S. These terms were intended to refer only to the mechanism, and not to the nervous system as a whole. The "initial" synapses are initial for the mechanism, but are not necessarily peripheral. The stimulus-intensity S is the magnitude of $\varepsilon - j$ applied to these synapses. The "terminal" synapses are those at which the mechanism develops the $\varepsilon - j$ which excites the efferent neurons leading to the effectors. With this understanding, let S and $S(1+\delta)$ be just completely discriminable. It is not necessary to repeat in this place the assumptions underlying the derivation of δ as a function of S, since these can be found stated in the previous paper D. We shall merely assume the result contained in equations (D 15), (D 16), (D 22) and (D 23):

$$\begin{gathered} u = 2\lambda S/3\,, \\ \delta = x + z\,, \\ ux^3 + x^2 - 1 = 0\,, \\ uz^3 - 2(x+1)z - (x+1)^2 = 0\,. \end{gathered} \tag{1}$$

The parameter λ measures the "strength" of the inhibitory neurons acting among the terminal synapses.

By assuming S to be proportional to the intensity of the peripheral stimulus, it was found that the theoretical curves agreed reasonably well with experimental data for light, sound, and touch. Moreover, only one parameter is involved, this parameter being the product of λ and the factor of proportionality connecting S with the peripheral stimulus, R. It was pointed out, however (D, p. 52), that this assumption of proportionality would certainly require modification, and that some analysis of the peripheral mechanism would be required, in general, to yield the true Weber-function. The organs of sight and hearing scarcely lend themselves to such treatment at present, for at least the intervention of visual purple, in the one case, and the organ of Corti, in the other, introduce unknown factors between the intensity of the adequate stimulus and the actual intensity of stimulation of the first-order neurons. The stimulation of the afferent fibers in muscle, however, seems to be much more direct, and in any case B. H. C. Matthews (1933) finds experimentally an approximately logarithmic relation between the tension and the frequency of response.

Suppose, then, that a weight is held motionless for a short time in, say, the open palm, the forearm being supported so that only the wrist muscles are employed in supporting the weight. The following assumptions are believed at least to offer no points of conflict with Matthews' experimental findings:

i) Each receptor has acting upon it a stimulus-intensity R which is proportional in magnitude to the weight being tested plus the weight of the supporting member, in this case the hand.

ii) The response of any receptor of threshold h leads to the development of $S = \varepsilon - j$ at the initial synapses of the discrimination mechanism according to the equation

$$S_h = \log R/h \,. \tag{2}$$

iii) Thresholds of the receptors vary among themselves with a distribution function which is expressible either in the form

$$N(h) = \beta' \, h^n (\alpha - h)^m \,, \tag{3}$$

where n and m are positive integers, or, if the distribution is multimodal, as a sum of such functions. Here we suppose the distribution unimodal.

It follows that the total S developed at the initial synapses of the mechanism is

$$S = \int_0^R S_h N(h)\, dh = \beta' \int_0^R h^n (\alpha - h)^m \log \frac{R}{h}\, dh \,.$$

For convenience of calculation, note that a change of units for measuring R (and hence for measuring h) requires only a change in the value of the constants α and β'. Hence it is no restriction to take $\alpha = 1$. This defines what we may term the "neurological unit" of weight, which is the weight which just excites the end-organ of greatest threshold. Its determination in a given series of observations amounts to the determination of one variable parameter. Thus, in place of the last equation we may write

$$S = \beta' \int_0^R h^n (1 - h)^m \log \frac{R}{h}\, dh \,. \tag{4}$$

If we expand by the binomial theorem and integrate we obtain

$$S = \beta' R^{n+1} \sum_{p=0}^{m} (-1)^p \binom{m}{p} \frac{R^p}{(n+p+1)^2} \,, \quad R \leq 1 \,, \tag{5}$$

and

$$\begin{aligned} S &= \beta' \int_0^1 h^n (1 - h)^m \log \frac{R}{h}\, dh \\ &= \beta' \sum_{p=0}^{m} (-1)^p \binom{m}{p} \left\{ \frac{1}{(n+p+1)^2} + \frac{\log R}{n+p+1} \right\}, \quad R > 1 \,. \end{aligned} \tag{6}$$

By way of fixing the parameters m and n, it seems reasonable to suppose that the distribution function $N(h)$ will be tangent to the h-axis at the limits of the distribution, i.e., at $h = 0$ and at $h = 1$. This corresponds to Oberlin's assumption, referred to above, that this distribution should be nearly normal. We take the smallest integral values of m and n for which this is true, and therefore assume

$$n = m = 2 \,, \tag{7}$$

which gives

$$N(h) = \beta' h^2 (1 - h)^2 \,. \tag{8}$$

Then equation (5) becomes

$$S = \frac{\beta'}{1800} R^3 \,(72R^2 - 225R + 200) \,. \tag{9}$$

Since S is proportional to u by equation (1), then if we set

$$u = \iota^3 \tag{10}$$

we have, after introducing a new parameter, β,

$$1269\beta^3 \tau^3 = R^3(72R^2 - 225R + 200) . \tag{11}$$

The reason for the factor 1269 will become apparent.

For small δ and hence large u we have, from (D36), with sufficient accuracy,

$$\tau^3 \delta = 2\tau^2 + \frac{4}{3}\tau - \frac{2}{9} , \tag{12}$$

if we note that the τ introduced in the above equation (10) is the reciprocal of that employed in (D36). Hence if Δ is the Weber-ratio corresponding to the peripheral stimulus R we have

$$\begin{aligned} R^3(1+\Delta)^3 & [72R^2(1+\Delta)^2 - 225R(1+\Delta) + 200] \\ &= 1269\,\beta^3 \tau^3 (1+\delta) \\ &= 1269\,\beta^3 (\tau^3 + 2\tau^2 + \frac{4}{3}\tau - \frac{2}{9}) \\ &= 1269\,\beta^3 [(\tau + \frac{2}{3})^3 - \frac{14}{27}] . \end{aligned} \tag{13}$$

For $R = 1$ it follows from equation (11) that $27\,\beta^3 \tau^3 = 1$. Hence let

$$3\,\beta\,\tau = t \tag{14}$$

and obtain

$$R^3(72R^2 - 225R + 200)/47 = t^3 , \tag{15}$$

$$\begin{aligned} R^3(1+\Delta)^3 & [72R^2(1+\Delta)^2 - 225R(1+\Delta) + 200]/47 \\ &= (t + 2\beta)^3 - 14\,\beta^3 . \end{aligned}$$

We have assumed that δ is small and u large in order to be able to write the approximate formula (12). Moreover, the last two equations are only valid for R, $R(1+\Delta)$ and t on the range from 0 to 1. From equations (10) and (14) it follows therefore that $27\beta^3$ is equal to the reciprocal of the largest value of u on the range considered, and we may therefore safely neglect the term $14\beta^3$ on the right of the above equation. In fact in the experimental data to be considered later this term is of the order of 10^{-4}, whereas the other terms are of the order of unity. Hence we have

$$\begin{aligned} R^3(1+\Delta)^3 & [72R^2(1+\Delta)^2 - 225R(1+\Delta) \\ & + 200]/47 = (t + 2\beta)^3 . \end{aligned} \tag{16}$$

A still further, and final, simplification can be made as follows. Since equation (15) is valid only for R and t on the range from zero to unity we find that t can be expressed as a function of R with sufficient accuracy by the interpolation parabola,

$$t = 1.62R - .62R^2\,, \tag{17}$$

which gives the correct values $t = 0, .655$, and 1 for $R = 0, .5$ and 1 respectively. Similarly

$$t + 2\beta = 1.62R(1 + \Delta) - .62R^2(1 + \Delta)^2\,. \tag{18}$$

Hence, on subtracting (17) from (18) we find

$$2\,\beta = 1.62\,R\,\Delta - .62R^2\,\Delta(2 + \Delta)\,,$$

or

$$31R^2\,\Delta^2 + (62R - 81)R\,\Delta + 100\,\beta = 0\,. \tag{19}$$

We choose the root of the quadratic (19) from the fact that $\Delta = 0$, when $\beta = 0$, so that we have, finally,

$$R\,\Delta = \frac{81 - 62R - \sqrt{(81 - 62R)^2 - 12400\,\beta}}{62}\,, \tag{20}$$

or, if we set

$$\gamma = 12400\,\beta\,, \tag{21}$$

then

$$R\,\Delta = \frac{81 - 62R - \sqrt{(81 - 62R)^2 - \gamma}}{62}\,. \tag{22}$$

Evidently if Δ is to be real for the entire range including $R = 1$ we must have

$$\gamma \leq 361\,, \qquad \beta \leq 361/12400\,. \tag{23}$$

The minimum value of Δ is obtained from (19) by finding the smallest positive value of Δ for which the roots R of (19), expressed in terms of Δ, are real, i.e., the smallest positive Δ for which the discriminant of (19), regarded as a quadratic in R, is positive. This is

$$\Delta_{\min} = \frac{24800\,\beta}{6561 - 12400\,\beta} = \frac{2\,\gamma}{6561 - \gamma} \tag{24}$$

Evidently $\Delta_{\min}$ increases in γ (or β). This minimum value is given by

$$R_{\min} = \frac{81}{62(\Delta_{\min} + 2)} = \frac{6561 - \gamma}{10{,}044}\,, \tag{25}$$

which decreases in γ. Since the largest admissible value of γ is 361, the smallest value of $R_{\min}$ is $50/81 \doteq .62$. For $\gamma = 0$ we obtain the largest value of $R_{\min}$ which is $81/124 \doteq .65$. At the same time $\Delta_{\min}$ varies from its maximum value of $361/3100 \doteq .12$, for $\gamma = 361$, to its minimum of 0 for $\gamma = 0$. On differentiating the right member of (22) with respect to R it is easily seen that $R\,\Delta$ is monotonically increasing in R.

3. *The difference limen.* If W is the weight of the stimulus-object in grams, W_0 the weight of the supporting member (the hand), then R is proportional to $W + W_0$. We have then three variable parameters, viz., W_0, β (or γ), and this constant of proportionality. In complete form, we may write

$$W + W_0 = \mu R\,,$$

$$(W + W_0)\Delta = \frac{81\mu - 62(W + W_0) - \sqrt{[81\mu - 62(W + W_0)]^2 - \mu^2\gamma}}{62}\,; \qquad (26)$$

where $)W + W_0)\Delta$ is the experimentally measurable difference limen ΔW. However, W_0 is also experimentally measurable so that only two of the parameters, μ and γ, are incapable of direct determination.

Nevertheless W_0 is not ordinarily given, although one can certainly tell its order of magnitude from the weight of one's own hand. We present herewith a comparison of the theoretical curves with some experimental data obtained by A. H. Holway, Janet E. Smith and M. Zigler (1937) for unimanual weight discrimination. No attempt has been made to fit the data given by Oberlin (1934), which seem rather less regular, although Oberlin's curves seem to follow the same general course. Unfortunately in their experiments, Holway, Smith, and Zigler seem to have made no effort to rule out possible pressure cues, so that actually more than muscular sense is involved. Data are determined for the two hands separately by the three observers, giving six sets in all, for weights ranging from 100 g. to 1600 g. We may note that in graphing their own data these writers take the mean for the two hands of each observer, thus obtaining much greater regularity than is to be found in the separate sets.

We present, in the accompanying figure, the graphs of the data for the separate hands of each observer, as well as the graph of the mean for each observer, along with the graphs of the best fitting theoretical curves. The reason for presenting the graphs of the means is the following. If the sensitivity of the two hands is essentially independent of the "handedness" of the individual, the data for the two hands should be equivalent and the means would thus be more reliable

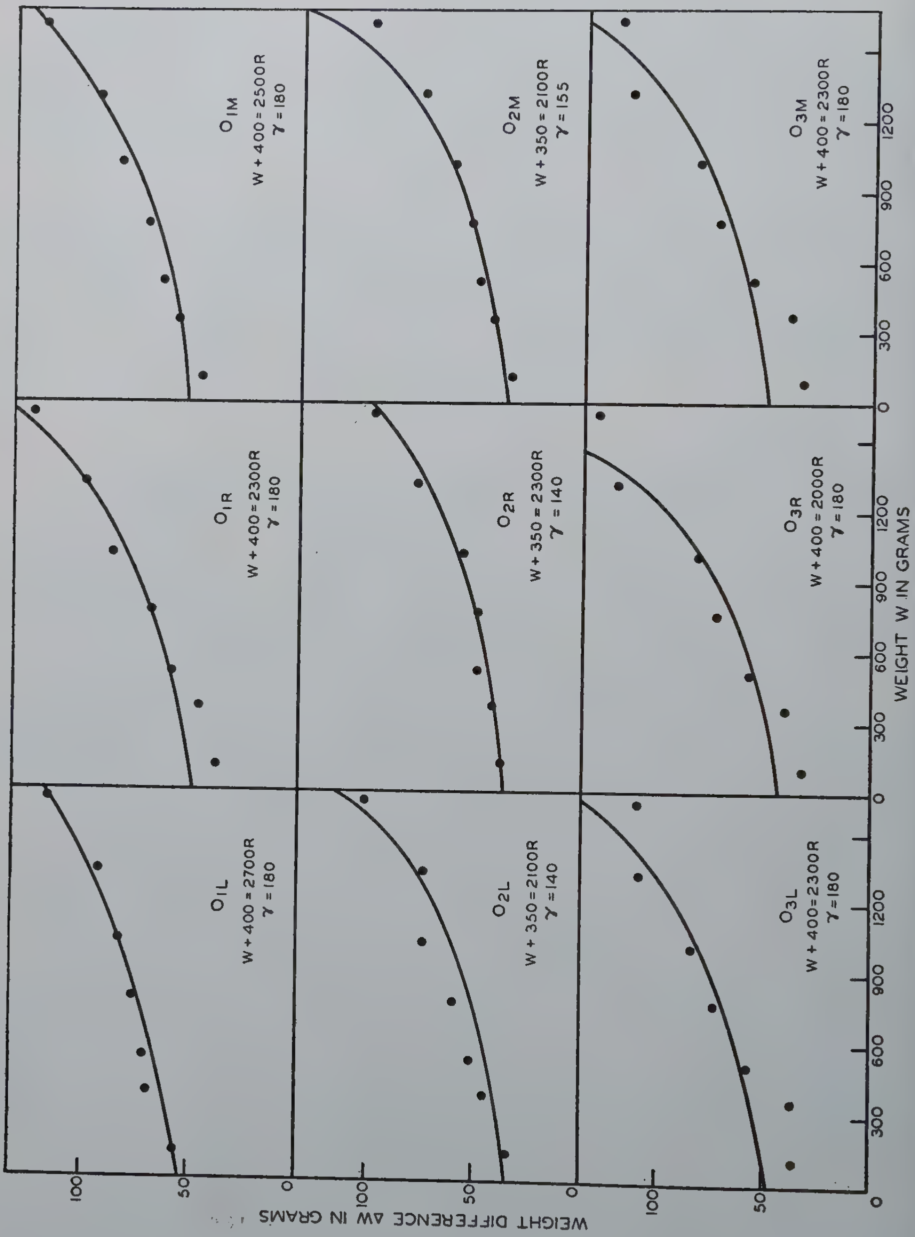
O1M
W + 400 = 2500R
γ = 180
O2M
W + 350 = 2100R
γ = 155
O3M
W + 400 = 2300R
γ = 180
O1R
W + 400 = 2300R
γ = 180
O2R
W + 350 = 2300R
γ = 140
O3R
W + 400 = 2000R
γ = 180
O1L
W + 400 = 2700R
γ = 180
O2L
W + 350 = 2100R
γ = 140
O3L
W + 400 = 2300R
γ = 180
0
300
600
900
1200
WEIGHT W IN GRAMS
100
50
0
WEIGHT DIFFERENCE ΔW IN GRAMS

FIGURE 1

since they were obtained from twice as many observations as were the data for the hands separately. And indeed, in the cases of observers 1 and 2 the greater regularity is at once apparent. We note further that the means for these observers also fit the theoretical curves much more closely than do the data for the separate hands. This is not true, however, for observer 3, where the points are equally irregular and the fits equally uncertain for the means and for the separate hands alike.

A mention of some of the steps in the determination of the parameters is relevant. Since the hand weights were not given, W_0 was determined along with μ and γ from the data for each hand separately, so as to obtain the best fitting theoretical curve. The theoretical curve was fitted to each of the six sets of data independently of the others, so that when the values of the parameters had been estimated for one hand of one observer, no account of these values was taken when the parameters for the other hand of the same observer were being estimated. Nevertheless, within the limits of accuracy allowed by the data, the values of W_0 for the two hands of the same observer came out the same in every case. Moreover, it turned out that for both of observers 1 and 3, the estimated value of W_0 was 400 g., whereas for observer 2, W_0 came out to be 350 g. Since observer 2 was a woman and the other two men it seems likely that she should, in fact, have smaller hands.

In fitting the curves to the averages, the values of W_0 were taken as known from the previous determinations, but μ and γ were determined independently. With each graph is given the values of the three parameters. The label O_{1L} means that this is the graph for the left hand of observer 1; O_{1M} signifies the mean for the two hands of observer 1; and similarly for the others.

It was pointed out above that the parameters μ and γ are not subject to a direct determination. However a word might be added by way of pointing out their physiological significance. It will be recalled that R is the ratio of the applied stimulus (hand-weight plus object-weight) to the maximum threshold of the sensitive elements. For $R = 1$, $W + W_0 = \mu$, so that $\mu - W_0$ is the least weight necessary to excite all the afferent fibers in the group utilized for the discrimination. It may be, however, that another group of fibers is present, possibly itself distributed according to a function of the form (3) but with different parameters and having a mode greater than the mode for the first group — greater, in fact, than $\mu - W_0$. If so the ΔW curve, which is rising rapidly where $W = \mu - W_0$, will level off somewhat for larger values of W. If not, either the increase in W will continue, and at an increasing rate, or else in effect the judgment will no longer be made with the wrist muscles alone and additional cues will be employed by the subject. These are questions for the experimenter to answer.

Whatever the case may be, the foregoing theoretical considerations indicate the need for the determination of additional difference limens under the following conditions:

1. When the wrist and finger muscles are not acting, nor yet the shoulder muscles, but only the elbow muscles.
2. When only the shoulder muscles are acting. In such experiments a plaster-of-paris cast such as the one employed by M. von Frey (1913) would doubtless be needed, so that purely tactile cues could be completely eliminated.

As for β (or γ), this is inversely proportional to the cube root of the value of u, equation (1), corresponding to $R = 1$. Hence the smaller the value of β the smaller the value of δ at $R = 1$, and thus β gives a measure of the fineness of the discriminal mechanism, a smaller β meaning a greater precision.

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AN APPROACH TO THE MATHEMATICAL BIOPHYSICS OF BIOLOGICAL SELF-REGULATION AND OF CELL POLARITY

N. RASHEVSKY
The University of Chicago

In a cell, in which the permeability to a metabolite is a function of the concentration of that metabolite, situations may occur, in which the diffusion field will exhibit certain assymetric patterns, even though the cell may possess geometrically spherical symmetry. This pattern results in a polarity of the cell. Moreover, the pattern being the result of a dynamic equilibrium, it possesses the property of self-regulation. Dividing the cell in two results in the appearance of a similar pattern in each half-cell.

Another case when such self regulation and polarity occur is given by considerations of the action of the diffusion forces upon colloidal particles, which affect catalytically the metabolic reactions. A simple case is treated mathematically.

The problem of biological self-regulation offers many different aspects. One of the most fundamental of these, and at the same time one of the most difficult is that of the development of regulation eggs. Most drastic interference with the visible internal structure of these eggs may leave them still capable of producing normal embryos (Harvey, E. B., 1932, 1936). Such self-regulation has perhaps been *the* phenomenon, upon which claims of the existence of non-physical elements in biology have been based. While much has been written on the physical aspects of self-regulation and it has been pointed out, that even relatively simple physico-chemical systems may at times possess the property of self-regulation, yet all these general considerations and analogies do not bring us much nearer to the solution of the problem. If we are to incorporate eventually these phenomena into the field of mathematical biophysics, we must proceed by studying *theoretical models, which are sufficiently specific* to be applied not only to the phenomenon of self-regulation in general, but to some definite biological case of it. Of course, when such a model is developed, it is by no means to be regarded as *the* explanation of the particular phenomenon, for which it is intended as a model. Most likely there is a large number of different possible explanations. It is only by studying systematically all theoretically possible cases and by a comparison of the mathematical deductions from each of those cases with available experimental data, that we may in the future arrive at a decision as to which, if any, of the theoretically studied situations actually occurs.

With this in mind, we shall now investigate a problem, which is suggested by such observations, as for instance those by E. B. Harvey (1932, 1936) on centrifuging *Arbacia* eggs. Subjecting them to a force 10,000 times that of gravity not only produces a definite stratification of the content of the egg, according to the specific gravity of the different constituents, but results eventually in a breaking up of the egg in two and even in four parts, each part containing *different* visible components. Yet, when fertilized, all four parts can give rise to normal embryos.

The early differentiation of the fertilized egg indicates definitely the preexistence of some sort of nonuniformities. At the same time these nonuniformities obviously cannot be connected with or even related to the visible material. Moreover, whatever latent nonuniformity pattern may have existed in the normal egg, the breaking of the latter into four parts of very different gross constitution must have resulted in each part acquiring again the same latent pattern, which characterized the original normal egg.

A suggestion has been made that the pattern responsible for the early differentiation is contained not in the cell volume, but on the surface in the cell membrane (Weiss, 1939). The latter being of a much more rigid nature than the more liquid interior of the egg, the centrifugal forces used in the experiment may not be sufficient to upset the inner structure of the membrane. Since there is a direct microscopic evidence for a superficial localization of the early noticeable differentiation of the egg (Weiss, 1939), it appears of interest to investigate this possibility more quantitatively.

It must however be remembered, that while there is good evidence for a more solid-like consistency of the egg membrane as compared with the interior of the egg, yet the membrane certainly cannot be considered as a solid bag, containing a liquid interior. For in such a case a force strong enough to break the egg into parts would simply tear the solid membrane, leaving the interior to flow out. The microphotographs taken by E. B. Harvey (1932, 1936) and reproduced by P. Weiss (Weiss, 1939, p. 191) show that under the influence of the centrifugal force the egg elongated and then divided by constriction in the middle. In other words the membrane at the equatorial region fuses together as only a liquid would do. If however the membrane is merely a very viscous liquid, sufficiently strong forces would upset its internal structure also.

I

Let us consider a spherical cell of radius r_0 cm., producing a substance at a constant rate q gm cm^{-3} sec^{-1}. Let the external concentration of the substance be c_0 gm cm^{-3} and the external diffusion coefficient D_e be very large, so that we may put $D_e = \infty$. This merely simplifies the calculations, without introducing any essential limitations. Let the internal diffusion coefficient be D cm^2 sec^{-1}. Assume further, that the membrane of the cell is not uniform in its physical constitution and that therefore its permeability is not the same at every point. Let the structure of the membrane possess an axial symmetry, thus imparting a polarity to the cell. Let at one pole the permeability have the value h_1 cm sec^{-1}, while at the other pole let that value be h_2 cm sec^{-1}. Due to such a nonuniform and asymmetric distribution of the permeability, the distribution of concentration of the produced substance within the cell will also not be spherically symmetric. In particular the concentration inside the cell at the membrane will vary from point to point.

To calculate the average concentration distribution in such a cell we shall use the usual approximation method (Rashevsky, 1940). Let $\bar{h}_1$ denote the *average* permeability in one hemisphere (Fig. 1), while

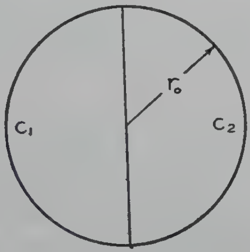

FIGURE 1

$\bar{h}_2$ denotes the average permeability in the other one. Correspondingly we shall denote by c_1 and c_2 the *average* concentrations *at the membrane* inside the cell in each hemisphere. Denoting by $\bar{c}$ the average concentration within the cell, we have

$$2D\frac{\bar{c}-c_1}{r_0} = \bar{h}_1(c_1 - c_0)\ ; \tag{1}$$

$$2D\frac{\bar{c}-c_2}{r_0} = \bar{h}_2(c_2 - c_0)\ ; \tag{2}$$

$$\frac{4}{3}\pi r_0{}^3 q = 2\pi r_0{}^2 \times 2D\frac{\bar{c}-c_1}{r_0} + 2\pi r_0{}^2 \times 2D\frac{\bar{c}-c_2}{r_0}\,. \tag{3}$$

Equations (1) and (2) give:

$$c_1 = \frac{2D\bar{c} + r_0\bar{h}_1 c_0}{2D + r_0\bar{h}_1}\,; \qquad c_2 = \frac{2D\bar{c} + r_0\bar{h}_2 c_0}{2D + r_0\bar{h}_2}\,. \tag{4}$$

Hence

$$\bar{c} - c_1 = \frac{r_0\bar{h}_1(\bar{c} - c_0)}{2D + r_0\bar{h}_1}\,; \qquad \bar{c} - c_2 = \frac{r_0\bar{h}_2(\bar{c} - c_0)}{2D + r_0\bar{h}_2}\,. \tag{5}$$

Introducing equation (5) into equation (3), we find after rearrangements:

$$\bar{c} = c_0 + \frac{r_0 q}{3\,D}\,\frac{(2D + r_0\bar{h}_1)(2D + r_0\bar{h}_2)}{\bar{h}_1(2D + r_0\bar{h}_2) + \bar{h}_2(2D + r_0\bar{h}_1)}\,. \tag{6}$$

For $\bar{h}_1 = \bar{h}_2 = h$, that is for a uniform membrane, equation (6) reduces to

$$\bar{c} = c_0 + \frac{q r_0}{3\,h} + \frac{q r_0^2}{6\,D}\,, \tag{7}$$

as should be the case*.

Equation (6) introduced into equation (4) gives

$$c_1 = c_0 + \frac{2r_0 q}{3}\,\frac{2D + r_0\bar{h}_2}{\bar{h}_1(2D + r_0\bar{h}_2) + \bar{h}_2(2D + r_0\bar{h}_1)}\,;$$

$$c_2 = c_0 + \frac{2r_0 q}{3}\,\frac{2D + r_0\bar{h}_1}{\bar{h}_1(2D + r_0\bar{h}_2) + \bar{h}_2(2D + r_0\bar{h}_1)}\,. \tag{8}$$

Thus an asymmetry of the cell membrane will result in an asymmetry of the diffusion field within the cell. For the approximate calculation of this field we considered two discrete *average* values $\bar{h}_1$ and $\bar{h}_2$ of the permeability. The actual value of the permeability is assumed to vary continuously along the meridian. If this variation is monotonic, then a division of the cell into several parts by sections parallel to the equator will produce smaller cells, each having a similar polarity.

We have here a model which may reproduce some of the properties of actual cells. Yet this model does really not show any regulation. It is essentially a "mosaic" model, the mosaic being attributed to the membrane and possessing a rather simple pattern. The above considerations suggest however an interesting possibility of actual regulation, which we shall mention here.

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* The equations derived for a spherically symmetrical cell previously (Rashevsky, 1940) differ from equation (7) in the values of the numerical coefficients, which are respectively 2/9 and 1/9. This is due to the fact that we considered there actually a cylinder whose length equals its diameter.

Suppose that the permeability h of the membrane is itself influenced by the concentration c of the metabolite in its vicinity. Such a supposition is biologically rather plausible. Let this influence be such, that an increase of c results in a decrease of h. Let the permeability be originally uniform all over the membrane. Then the diffusion field will possess spherical symmetry. Let now the concentration become, because of some disturbance, slightly higher at one region of the membrane. This will result is a decrease of permeability in that region, thus creating a condition similar to the one discussed above. But in that case the concentration c at the membrane will be larger in the region with smaller h. This can be readily seen from equations (8), which give:

$$c_1 - c_2 = \frac{2r_0{}^2q(\bar{h}_2 - \bar{h}_1)}{\bar{h}_1(2D + r_0\bar{h}_2) + \bar{h}_2(2D + r_0\bar{h}_1)} \,. \tag{9}$$

Equation (9) shows, that when $\bar{h}_1 < \bar{h}_2$, then $c_1 > c_2$. Thus the resulting change in permeability will result in a further increase of c at that place, thus enhancing the asymmetry. We may ask whether under such conditions stable asymmetric configurations may not be obtained.

Mathematically the problem reduces to the following. Let h be a prescribed function of c, $h = f(c)$. We then have $\bar{h}_1 = f(c_1)$ and $\bar{h}_2 = f(c_2)$. Denote the right hand side of the first equation (8) by $u_1(h_1, h_2)$ and the right hand side of the second equation (8) by $u_2(\bar{h}_1, \bar{h}_2)$. Then, since $\bar{h}_1$ and $\bar{h}_2$ are functions of c_1 and c_2, we find that $u_1(\bar{h}_1, \bar{h}_2) = u_1[f(c_1), f(c_2)] = v_1(c_1, c_2)$; and similarly $u_2(\bar{h}_1, \bar{h}_2) = v_2(c_1, c_2)$. We must now look for *stable* solutions of the system of equations:

$$\begin{aligned} c_1 &= v_1(c_1, c_2), \\ c_2 &= v_2(c_1, c_2), \end{aligned} \tag{10}$$

other than $c_1 = c_2$, which corresponds to a spherical symmetry. It can be shown that when $f(c)$ is monotonic, only spherically symmetric solutions are possible. Physically this is due to the fact that when an asymmetric configuration is obtained in a manner described above, then any slight increase of c at the *lower* end will result in a decrease of h at that end, with a resulting further increase of c, until it reaches the same value as at the higher end. However we cannot *a priori* exclude the possibility that for some special types of the function $f(c)$ asymmetric solutions of the system (10) may exist. The problem now is to investigate whether this is possible and if so, for what forms of $f(c)$. Furthermore we shall have to ascertain, that if such possibilities exist, the necessary form of $f(c)$ is biologically plausible or at least possible.

For given $\bar{h}_1$ and $\bar{h}_2$, the values $c_1 = u_1(\bar{h}_1, \bar{h}_2)$ and $c_2 = u_2(\bar{h}_1, \bar{h}_2)$, as expressed by equations (8), are obtained by considerations of material balance in a stationary state. Therefore when $c_1 > u_1$, c_1 will decrease until it reaches the value u_1. Conversely if $c_1 < u_1$, c_1 will increase until it reaches the value u_1. A similar thing holds for c_2. Therefore the conditions of stability require that any small increment of c_1 would result in a lesser increment of $u_1(\bar{h}_1, \bar{h}_2)$ or, which is the same, of $v_1(c_1, c_2)$, so that $\partial v_1/\partial c_1 < 1$; and similarly $\partial v_2/\partial c_2 < 1$. For the symmetrical case, when $c_1 = c_2$, it may happen that the configuration will be stable for a simultaneous equal increase or decrease of c_1 and c_2, but unstable for an increase of c_1 accompanied by a decrease of c_2 or vice versa.

If asymmetric stable solutions of the system (10) exist for some forms of $f(c)$, and if they exist for a sufficiently large range of values of r_0, then we have a case of a true self-regulation. No matter how we divide such a cell, whether equatorially or meridionally, no matter how we stir up its content, the cell or each part of it within the admissible range of r_0, will automatically reconstitute the asymmetry of the diffusion field.

We have however rather formulated a problem than given a solution. A consideration of a different physical mechanisms leads us to a simpler solution of this type of problem.

II

Consider again a spherical cell, producing a substance. Let however now the permeability be a constant, h. Let moreover the cell contain a catalyst, which *inhibits* the reaction, so that the higher the concentration n of the catalyst, the smaller the rate of production q. If the molecules of the catalyst are rather large, or if the latter is present in a colloidal state, with a particle size $> 2 \times 10^{-7}$ cm., then as we have seen elsewhere (Rashevsky, 1938), due to the action of the diffusion forces, these particles will show a pronounced nonuniformity of distribution, their concentration n being larger in regions of smaller concentrations c of the diffusing metabolite. For a produced substance, when the negative gradients are directed outwards, the catalyst will accumulate at the periphery, decreasing there the rate of production and still enhancing the gradient of c. However, for a spherically symmetric distribution of the catalyst, everything will remain spherically symmetric and the *average* rate of production q will be the same in any arbitrarily chosen half of the cell. If however, for some reason, in one of the hemispheres the average concentration $\bar{c}$ increases, this will result in an increase of n in the other hemisphere at the expense of the first. This will cause a further increase of $\bar{c}$ in the first hemisphere, enhancing the asymmetry. To investigate the possibilities in this case, let us first investigate what effect a variation of q from point to point in a cell will have upon the diffusion field.

Referring again to Fig. 1, denote the *average* concentration *in one hemisphere* by $\bar{c}_1$, in the other by $\bar{c}_2$. Denote the average rate of production in the first hemisphere by q_1, in the second by q_2. We now have

$$2D\frac{\bar{c}_1 - c_0}{r_0} = h(c_1 - c_0) \; , \tag{11}$$

$$2D\frac{\bar{c}_2 - c_2}{r_0} = h(c_2 - c_0) \; . \tag{12}$$

The material balance equation is now however somewhat modified. Due to the different values of $\bar{c}$ in the two hemispheres, there will now be not only an outflow of the metabolite from the cell, but also an inner flow, from one hemisphere to another. Since the average gradient for this flow is approximately $(\bar{c}_1 - \bar{c}_2)/r_0$, and the area through which the flow takes place is πr_0^2, that of the equatorial circle, the total inner flow is equal to $\pi r_0 D(\bar{c}_1 - \bar{c}_2)$. We now have for the first hemisphere

$$\frac{2}{3}\pi r_0^3 q_1 = 2\pi r_0^2 \times 2D\frac{\bar{c}_1 - c_1}{r_0} + \pi r_0 D(\bar{c}_1 - \bar{c}_2) \; , \tag{13}$$

and for the second

$$\frac{2}{3}\pi r_0^3 q_2 = 2\pi r_0^2 \times 2D\frac{\bar{c}_2 - c_2}{r_0} - \pi r_0 D(\bar{c}_1 - \bar{c}_2) \; . \tag{14}$$

Equations (11) and (12) give

$$c_1 = \frac{2D\bar{c}_1 + r_0 h c_0}{2D + r_0 h} \; ; \quad c_2 = \frac{2D\bar{c}_2 + r_0 h c_0}{2D + r_0 h} \; . \tag{15}$$

Introducing (15) into equations (13) and (14) we find after rearrangement:

$$\begin{aligned} 3D(2D+5r_0h)\bar{c}_1 &= 3D(2D+r_0h)\bar{c}_2 \\ &\quad + 12Dr_0hc_0 + 2(2D+r_0h)r_0^2q_1\,; \\ 3D(2D+5r_0h)\bar{c}_2 &= 3D(2D+r_0h)\bar{c}_1 \\ &\quad + 12Dr_0hc_0 + 2(2D+r_0h)r_0^2q_2\,. \end{aligned} \tag{16}$$

Solving we find:

$$\begin{aligned} \bar{c}_1 &= c_0 + \frac{r_0^2(2D+r_0h)\,[(2D+r_0h)q_2 + (2D+5r_0h)q_1]}{12Dr_0h(2D+3r_0h)}\,, \\ \bar{c}_2 &= c_0 + \frac{r_0^2(2D+r_0h)\,[(2D+r_0h)q_1 + (2D+5r_0h)q_2]}{12Dr_0h(2D+3r_0h)}\,. \end{aligned} \tag{17}$$

Hence

$$\bar{c}_1 - \bar{c}_2 = \frac{r_0^2(2D+r_0h)(q_1 - q_2)}{3D(2D+3r_0h)}\,. \tag{18}$$

The difference $\bar{c}_1 - \bar{c}_2$ vanishes for $q_1 = q_2$. When $q_1 > q_1$, then $\bar{c}_1 > \bar{c}_2$.

Now let us investigate the effect of such an asymmetric concentration distribution of the metabolite upon the concentration n of the catalyst. Denoting by V the volume of the particle, by N — Avogradro's number, and by M — the molecular weight of the diffusing metabolite, and putting

$$\alpha = \frac{3}{2}\frac{NV}{M}\,, \tag{19}$$

we have (MB, p. 67), for the ratio n_1/n_2 of the concentrations of the catalyst in the two hemispheres

$$\frac{n_1}{n_2} = e^{-\alpha(\bar{c}_1 - \bar{c}_2)}\,. \tag{20}$$

Denoting by n the average concentration of the catalyst in the whole cell, and remembering that the total amount of the catalyst $\frac{4}{3}\pi r_0^3 n$ is constant, we have

$$n = \frac{n_1 + n_2}{2}\,. \tag{21}$$

Putting

$$\bar{c}_1 - \bar{c}_2 = x\,, \tag{22}$$

we find from equations (20) and (21)

$$n_2 - n_1 = 2n \tanh \tfrac{1}{2}\alpha x \, . \qquad (23)$$

For the effect of the catalyst on the reaction rate q let us consider the simplest possible relation, a linear one.
Let

$$q = q_0 - an \, , \qquad (24)$$

where a is a constant. Then

$$q_1 - q_2 = a(n_2 - n_1) \, . \qquad (25)$$

If an asymmetric distribution is to be possible, it must be represented by a stable root of the equation, obtained by introducing (23) into (25) and then introducing the latter into (18). Putting

$$\frac{r_0^2(2D + r_0 h)}{3D(2D + 3r_0 h)} = A \; , \qquad (26)$$

we thus find

$$x = 2Aan \tanh \tfrac{1}{2}\alpha x. \qquad (27)$$

If, as will usually be the case, αx is rather small, we may expand the hyperbolic tangent keeping only the lowest nonvanishing power. Equation (27) then becomes

$$x = Aan\alpha x\left(1 - \frac{1}{12}\alpha^2 x^2\right) \; , \qquad (28)$$

which, besides $x = 0$, has a positive root:

$$x^* = \frac{2}{\alpha}\sqrt{\frac{3(Aan\alpha - 1)}{Aan\alpha}} \; , \qquad (29)$$

provided

$$Aan\alpha > 1 \, . \qquad (30)$$

That the root (29) corresponds to a stable configuration is seen by graphing equation (28). The curve which represents the right hand side of (28), is nothing else but the right hand side of equation (18). By a similar argument as before we must have for stability

$$\frac{d}{dx} Aan\alpha x\left(1 - \frac{1}{12}x^2\alpha^2\right) < 1 \quad \text{for} \quad x = x^*$$

which is actually the case.

The model discussed here does exhibit true selfregulation. No matter how the cell is divided or how its content is stirred, the characteristic asymmetry of the diffusion gradient will be automatically reestablished. By considering the presence of several catalysts with different particle size, and affecting different reactions, we may obtain complex asymmetric patterns of the diffusion field, which thus may represent a rather intricate latent self-regulating structure.

It must be noted that the diffusion force per unit volume, $-(RT/M)$ grad c may be of the order of $10^7 - 10^8$ dyn. cm^{-3}, (Rashevsky, 1938), which is not only comparable, but even may exceed the centrifugal forces used in the above mentioned experiments. Moreover while the effect of the centrifugal forces upon a particle is proportional to the difference in specific weights of the particle and of the surrounding liquid and vanishes when the two specific weights become identical, no such restriction holds for the effect of diffusion forces. The model discussed here may in principle be mutilated beyond the point when self-regulation is possible, by applying such a strong centrifugal force, that all the catalyst is driven into one cell fragment. But this may require centrifugal forces far in excess of those available now.

III

Another important result of this study is that it leads us into the theory of cell polarity. A cell like the one discussed in section II always possesses a "polarity," and it is known that polarity is rather the rule in cell biology. The asymmetric distribution of the metabolite and therefore of the diffusion forces will in general result in asymmetries of all other important physical properties of the cell. Aggregates of such polar cells will themselves exhibit polar properties and a way is thus indicated for a mathematical biophysics of different types of tissues.

A polarity considered in section II is of a dynamic nature. But due to the irreversibility of some biological reactions, it may result after a lapse of time in a permanent polarity of a static nature, as discussed in section I.

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CONTRIBUTIONS TO THE MATHEMATICAL BIOPHYSICS OF ORGANIC FORM

I. FORMATION OF CAVITIES IN CELLULAR AGGREGATES

N. RASHEVSKY
The University of Chicago

The action of diffusion forces in aggregates of metabolising cells is studied mathematically, and it is shown that under definite conditions these forces may lead to the formation of inner cavities inside of the cellular aggregate. Different quantitative relations are derived and the possible bearing of these results on some embryological phenomena is discussed. A possible application of these considerations to the theory of formation of vacuoles is also discussed.

In our previous studies (for a summary see Rashevsky 1938 and 1940; hereinafter referred to as MB and A, correspondingly) we have discussed various dynamic aspects of the action of metabolic diffusion forces upon the cell. We have only occasionally touched the dynamics or even statics of cellular aggregates. In this paper we propose to study some of those omitted questions.

We have seen that in any cell with positive effective metabolism (A, chapter iii), the diffusion forces are directed outward and in the case of any deviation of the cell from spherical shape, a situation which is always present, those forces result in the elongation and eventual division of the cell. As has been remarked in MB, chapter viii, in principle we may consider also those effects of the forces which tend to simply disrupt, to burst, or to expand the cell. If we consider the cell as we have done hitherto, as a liquid system, then due to the practical incompressibility of liquids such an expansion would require forces much larger than those which may be produced by diffusion. If on the other hand we consider the expansion of the cell as merely the expansion of its membrane, followed by a free flow of water from outside into the increased volume bounded by the membrane, then such an expansion becomes quite possible under the action of diffusion forces, and its study leads to some interesting aspects of cell growth (A, chapter iv).

A somewhat different situation is possible when we consider not a single cell, but an aggregate of cells. If such an aggregate has a positive effective metabolism, then the individual cells of the aggregate repel each other. If nothing holds these cells together, then they simply would separate and disperse under the action of the diffusion forces. If however the aggregate is held together, for instance by an elastic membrane in which it is enclosed, or by forces of surface adhesion, which makes the cells stick to each other, then this membrane will oppose a complete scattering of the cells. The cells may however move apart to some extent, stretching the membrane. Since the volume of each individual cell remains constant, such a moving apart will result in the formation of a cavity inside the aggregate. If the aggregate is approximately spherical, this will result in the formation of a hollow spherical shell. Such a shell need not consist of a single layer of cells. The thickness of the shell and its overall size will be determined by the equilibrium between the diffusion forces of repulsion and the elastic forces of the membrane, which tend to counteract the forces of repulsion.

To establish the conditions of equilibrium, we must first of all calculate the work done by the diffusion forces when the shell expands, becoming thinner. Denoting by r_1 the radius of the cavity, by r_2 the external radius of the shell ,we see that in such an expansion both r_1 and r_2 increase. Since however the total volume V of all the cells remains constant, we have

$$\frac{4}{3}\pi(r_2^3 - r_1^3) = V \, , \tag{1}$$

Putting

$$a = \frac{3V}{4\pi} \, , \tag{2}$$

we may write

$$r_2^3 - r_1^3 = a \, , \tag{3}$$

or

$$r_1 = \sqrt[3]{r_2^3 - a} \, . \tag{4}$$

On each element of volume of the shell there acts a force (A, chapter iii)

$$F = -\frac{3}{2}\frac{RT\mu}{\overline{M}} \operatorname{grad} c \, , \tag{5}$$

the notations being the same as in A . Moreover, at the outer surface of the shell there acts a force due to the difference of concentrations on both sides of the membrane. Without introducing any fundamental restrictions, we may consider a case in which this surface force is negligible, due to a large permeability of the membrane. This merely simplifies the final expressions.

The total work done in any deformation of the aggregate by the force (4) is equal to (MB, p. 74):

$$\delta W = -\frac{3}{2}\frac{RT\mu}{M}\int_0^V \mathfrak{v} \operatorname{grad} c_i d\tau \,, \tag{6}$$

where $\mathfrak{v}$ is the displacement of the element of volume $d\tau$ and c_i the internal concentration. But

$$\int \mathfrak{v} \operatorname{grad} c_i d\tau = -\int_V c_1 \operatorname{div} \mathfrak{v}\, d\tau + \int_S c_S \bar{\mathfrak{v}}\, dS \,, \tag{7}$$

where c_s denotes the concentration at the surface which bounds the volume V of the aggregate, $\bar{\mathfrak{v}}$ denotes the value of $\mathfrak{v}$ at the surface and dS is the element of the surface.

Since in the deformation of the type considered here not only the total volume V remains constant, but also the volume of every individual cell is considered as constant, $\operatorname{div} \mathfrak{v} = 0$, and (5) and (7) give:

$$\delta W = -\frac{3}{2}\frac{RT\mu}{M}\int_S c_s \bar{\mathfrak{v}}\, dS \,. \tag{8}$$

A spherical shell is bounded by two surfaces: the inner sphere of radius r_1 and the outer one of radius r_2. The integral in (8) consists therefore of two parts. Denoting the concentration at the inner surface by c_1, that at the outer by c_2, and remembering that the outward directions of the normals at the two surfaces are opposite and that therefore at the inner surface $\bar{\mathfrak{v}} = -dr_1$, while at the outer surface $\bar{\mathfrak{v}} = dr_2$, we find that the integral in (8) is equal to

$$-4\pi r_1^2 c_1 dr_1 + 4\pi r_2^2 c_2 dr_2 \,. \tag{9}$$

Since during the deformation considered the volume of the shell remains constant, $4\pi r_1^2 dr_1 = 4\pi r_2^2 dr_2$. Hence, combining (9) with (8) we obtain:

$$\delta W = \frac{6\pi RT\mu}{\overline{M}} r_2^2 (c_1 - c_2)\, dr_2 \,. \tag{10}$$

The quantity $(c_1 - c_2)$ may be easily obtained for a perfectly spherical shell by integrating the diffusion equation. Since however there are no perfect spheres anyway, we shall use the usual approximation method (A, chapter i) and save considerable calculations.

Since we consider the case of positive effective metabolism, we have $c_1 > c_2$, and the total ouflow is equal to

$$\frac{4\pi r_2^2 \bar{D}_i (c_1 - c_2)}{r_2 - r_1} \,, \tag{11}$$

D_i denoting the internal diffusion coefficient.

The total production equals for a case of constant rate of production:

$$V\bar{q} = \frac{4}{3}\pi a\bar{q} \, . \tag{12}$$

Putting (11) equal to (12), solving with respect to $c_1 - c_2$ and substituting into (10) we have

$$\delta W = \frac{2\pi RT\mu q a(\bar{r}_2 - r_1)}{\bar{M}\,\bar{D}_i} dr_2 \, . \tag{13}$$

Now we must calculate the work done by the elastic forces of the membrane, when it is stretched due to an increase of the radius of the shell from r_2 to $r_2 + dr_2$. Assuming the membrane to behave like an elastic body, the work done will be equal to $\varepsilon dS/S$, where ε is a constant similar in nature to the modulus of elasticity. Since $S = 4\pi r_2^2$, $dS = 8\pi r_2 dr_2$ therefore the work done by the elastic forces of the membrane is equal to

$$\delta W = -\frac{2\varepsilon}{r_2} dr_2 \, . \tag{14}$$

The shell will be mechanically in equilibrium, when the sum of (13) and (14) is zero. Writing down this requirement, substituting in (13) for r_1 its expression (4) and putting

$$K = \frac{\bar{M}\,\bar{D}_i\varepsilon}{\pi RT\bar{q}\mu} \, , \tag{15}$$

we find

$$a r_2 (r_2 - \sqrt[3]{r_2^3 - a}) = K \, . \tag{16}$$

For any given value of a, or what amounts to the same, for any given value of V, equation (16) gives us the corresponding value of r_2 and because of (4), also the value of r_1. Unfortunately equation (16) is not conveniently solved in closed form. A discussion of it is however of interest. Physically r_2 cannot be smaller than $\sqrt[3]{a}$. This corresponds to $r_1 = 0$, that is to the absence of any cavity. If for a value of a the largest root of equation (16) is less than $\sqrt[3]{a}$, this means that for this value of a the stable configuration is that of a compact aggregate of cells, without any other inner cavities. This is due to the fact that in this case the volume of the aggregate is still so small, that the gradients of concentration and therefore the diffusion forces are not large enough to overcome the elastic forces of the membrane. As the volume of the aggregate increases, these forces increase, and for a critical volume V^*, to which corresponds the value a^* of a, the diffusion forces will just balance the elastic forces. For this volume we have $r_2^3 = a$, or $r_2 = \sqrt[3]{a}$. As the volume increases further, a cavity is formed and $r_2 > \sqrt[3]{a}$.

The value a^* can be found by putting in equation (16) $r_2 > \sqrt[3]{a}$ and solving the latter for a. We then find:

$$a^* = K^{3/5} = \sqrt[5]{\left(\frac{\bar{M}\,\bar{D}_i\varepsilon}{RT\bar{q}\mu}\right)^3}\,. \tag{17}$$

The outside radius r_2 is in this case equal to

$$r_2{}^* = \sqrt[5]{\frac{M\,D_i\varepsilon}{RT\bar{q}\mu}} = \sqrt[5]{K}\,. \tag{18}$$

Equation (18) gives us the size of the cell aggregate above which it will not remain closely packed, but will form a hollow shell.

Instead of varying the size of the aggregate we may keep it constant and vary any one of the other parameters, for instance q. As long as $r_2 < \sqrt[5]{K}$, the cellular aggregate is a closely packed one, there are no cavities and $r_1 = 0$. If we keep $r_2 = r_0$ constant, but increase q, then K will decrease and eventually we shall have $r_0 > \sqrt[5]{K}$. As soon as this happens a cavity will be formed, and $r_2 = r_0$ will increase due to the expansion of the whole structure. The size of the cavity will be determined by (4) into which the positive root of equation (16) is to be substituted for r_1.

If instead of an elastic membrane we consider the outside membrane as a liquid film with the surface tension γ erg cm^{-2} we obtain a somewhat different result. The work done by the surface tension is equal to $-\gamma\, dS = -8\pi\gamma r_2 dr_2$. Using this instead of (14) we now find instead of (16):

$$a(r_2 - \sqrt[3]{r_2^3 - a}) = K' r_2 \quad ; \quad K' = \frac{4\,\bar{M}\,\bar{D}_i\,\gamma}{RT\bar{q}\mu}\,. \tag{19}$$

Equation (19) may be written

$$(a - K')\,r_2 = a\sqrt[3]{r_2^3 - a}\,. \tag{20}$$

Raising both sides to the third power and solving for r_2, we find:

$$r_2 = \sqrt[3]{\frac{a^4}{a^3 - (a - K')^3}}\,. \tag{21}$$

Since again $r_2^3 \geqslant a$, we find the critical value a^* for which $r_2^3 > a$ from

$$\frac{a^4}{a^3 - (a - K')^3} = a \; ,$$

which gives

$$a = K' \, . \tag{22}$$

The corresponding value of r_2^* is

$$r_2^* = \sqrt[3]{K'} = \sqrt[3]{\frac{4\,\bar{M}\,\bar{D}_i\,\gamma}{RT\bar{q}\mu}} \; , \tag{23}$$

an expression analogous to that for the critical radius of a cell, above which it divides (MB, chapter viii; A, chapter iii).

II

As another interesting theoretical possibility we shall investigate a case of formation of cavities due to the inter-play of diffusion forces only, in the absence of any elastic membranes.

Consider again a densely packed cellular aggregate, consuming at a constant rate per unit volume oxygen supplied from outside. The concentration of oxygen decreases from periphery to the center and cells closer to the center have a smaller "external" oxygen concentration, than cells closer to periphery.

It has been shown by H. D. Landahl (1939) that the glycolytic coefficient of a cell (A, p. 34) increases with decreasing external oxygen concentration (A, p. 36). On the other hand, we have shown that the effective metabolic rate is a linear function of the glycolytic coefficient β, of the form

$$\bar{q} = A\beta + B \quad ; \quad A > 0 \quad ; \quad B \gtrless 0 \, . \tag{24}$$

When $B < 0$, $\bar{q}$ is zero for a positive value of $\beta = -B/A$, positive for $\beta > -B/A$ and negative for $\beta < -B/A$. But a change in the sign of $\bar{q}$ means a reversal of the direction of osmotic forces, which are forces of attraction for $\bar{q} < 0$ and forces of repulsion for $\bar{q} > 0$. (A, chapter iii).

With a sufficiently large supply of oxygen to the cellular aggregate, the cells nearer to the periphery may have a sufficiently small β to give $\bar{q} < 0$, and will attract each other, while the inner cells, with a smaller supply of oxygen, may have a large enough β to make $\bar{q} > 0$, and will repel each other. Thus within the same aggregate we shall have a system of two opposite forces, one tending to expand the aggregate, the other tending to keep it together. In a sense we may say, that the outer layer of the mutually attracting cells now plays the role of an elastic membrane, that holds together the inner cells, which repel each other. If the repelling forces prevail the aggregate will expand, forming a cavity. But due to this expansion the thickness of the layer of cells, forming the hollow shell, will decrease. Therefore the inner cells will receive more oxygen than before, their glycolytic coefficient β will decrease and the repelling force will decrease. An equilibrium is reached, when the two forces just compensate each other.

To determine the equilibrium configuration we must again calculate the work done in an infinitesimal expansion of the spherical shell. The system is in equilibrium when that work is zero.

The forces in the present case are again derived from a potential, although this potential is not connected with the concentration of the oxygen alone. Since somewhere between $r = r_1$ and $r = r_2$ the force is zero, the potential has a minimum at that place. By an argument, similar to that which leads to equation (10), we find that the work done in an infinitesimal expansion of the shell vanishes when the potential of the effective force at $r = r_1$ is equal to the potential at $r = r_2$. But this means that the average gradient of the potential in the shell and hence the average force is zero. Approximately this means that the average concentration of oxygen in the shell is equal to that value c^*, for which $\beta = -B/A$. Hence in order to determine the equilibrium configuration of the cellular shell we must determine the configuration, for which the average oxygen concentration $\bar{c}'$ is equal to c^*.

The average concentration of oxygen $\bar{c}$ is determined again by considerations of material balance. Denoting by primes the constants that refer specifically to oxygen and remembering that for oxygen consumption $q' < 0$, we have for material balance

$$\frac{4\pi r_2^2 D'_i (c'_2 - c'_1)}{r_2 - r_1} = \frac{4}{3}\pi a q' \tag{25}$$

which gives

$$c'_1 = c'_2 - \frac{a q' (r_2 - r_1)}{3 D'_i r_2^2} . \tag{26}$$

Denoting by c'_0 the external concentration of oxygen and by D'_e its external diffusion coefficient, we have outside of the shell (A, chapter i, since $\delta = r_2$):

$$\frac{4\pi r_2^2 D'_e (c'_0 - c'_2)}{r_2} = \frac{4}{3}\pi a q' , \tag{27}$$

which gives

$$c'_2 = c'_0 - \frac{aq'}{3\,D'_e\,r_2}\,. \tag{28}$$

The average oxygen concentration $\bar{c}'$ is given by

$$\bar{c}' = \frac{c'_1 + c'_2}{2}\,. \tag{29}$$

From equations (26), (28) and (29) we have:

$$\bar{c}' = c'_0 - \frac{aq'}{3r_2D'_e} - \frac{aq'(r_2 - r_1)}{6D'_i r_2^2}\,. \tag{30}$$

Introducing now into equation (30) the expression (4) and writing the requirement of equilibrium $\bar{c}' = c^*$, we obtain after rearrangements

$$(2D'_i + D'_e)\,q'ar_2 - D'_e q'a\sqrt[3]{r_2^3 - a} = Lr_2^2\ ;\ L = 6D'_iD'_e(c'_0 - c^*)\,. \tag{31}$$

This equation determines r_2 for every given a in terms of the other parameters. We have however the same difficulty as with equation (16). An exact expression for r_2 in closed form is impossible. However by the same argument as before we find the critical value a^* of a above which a cavity begins to form, by putting in equation (31) $r_2 = \sqrt[3]{a}$, and solving for a. This gives:

$$a^* = \left[\frac{6D'_iD'_e(c'_0 - c^*)}{2(D'_i + D'_e)\,q'}\right]^{3/2} \tag{32}$$

and

$$r_2^* = \sqrt{\frac{6D'_iD'_e(c'_0 - c^*)}{(2D'_i + D'_e)\,q'}}\,. \tag{33}$$

Putting $D_i \backsim D_e \backsim 10^{-7}$ cm^2 sec^{-1} ; $q' = 10^{-6}$ gm cm^{-3} sec^{-1}, and $c'_0 - c^* \backsim c'_0 \backsim 10^{-4}$ gm cm^{-3} we find

$$r_2 \backsim 10^{-2}\ \text{cm}\,.$$

III

The cases considered above are only two out of many other possible ones. We may study in a similar fashion situations, in which q is a function of concentrations and obtain still different expressions. The interesting point of this investigation is that it shows that under rather general conditions formation of inner cavities will occur in cellular aggregates. It is the embryologist who should be most interested in such studies, since formation of cavities of different sorts is an important feature of embryonic development.

It is of course highly unlikely, that all cases of formation of cavities are due to the same mechanism. But such an assumption is not even necessary. In fact we already have found two different mechanisms which lead to formation of cavities and a number of other mechanisms may still be found. If we eventually wish to find *the* mechanism, responsible for the formation of one or another type of cavities, the natural procedure to follow is to study all theoretically possible cases and then by comparing the theory with observation decide which of the possible cases actually do occur.

Consider for instance equations (18) and (33). While, as can be seen, they may roughly give the same value for the critical size at which the formation of cavity sets in, yet the dependence of this critical size on various external factors is very different in the two cases. While equation (18) involves only the effective metabolism and the effective values of $\bar{D}$ and $\overline{M}$, equation (33) involves the corresponding values for oxygen specifically. If one could for instance observe the onset of the formation of a cavity in a morula, leading to a blastula, under varying conditions which affect the oxygen consumption, the different diffusion coefficients, etc., one might perhaps decide in favor either of (18) or (33). Thus, further mathematical studies in that direction will undoubtedly suggest new experimental problems to the embryologist.

Speaking of the two cases discussed here, the case studied in section I seems to be more likely, particularly in the view of the fact that drugs inhibiting glycolysis do not seem to affect the formation of normal blastulae (Brachet, 1934). But one cannot entirely exclude the possibility of the other case. It is even possible that the two mechanisms may combine together.

Inasmuch as in case of a negative effective metabolism no cell division should occur (A, chapter iii, MB, chapter x), and particularly no mistoses in superficial layers should take place one might think that the case studied in section II can have no embryological applications. This conclusion is however not binding. In the outer layer the average $\bar{q}$ may be negative. But $\bar{q}$ will fluctuate from cell to cell, so that at every given moment some cells will have a positive $\bar{q}$, and will divide. In the layer as a whole however the attracting forces will prevail.

The following considerations may be of interest. In a single cell, considered as a sort of liquid drop, the formation of a cavity would require much stronger forces, because the inside of the cavity would be filled only with the saturated vapor of the cell liquids with a very low pressure, whereas the outside surface would be subject to atmospheric pressure. But if we consider the cell as a sack formed by the membrane and filled with colloidal metabolising particles, suspended in water (MB, chapter viii; A, chapter iii), then *formally* each particle will behave like a cell of an aggregate. These particles may well expand forming a sort of shell, with a cavity consisting of water free of particles and containing only nonmetabolising products. We would thus have a cell consisting of an outer metabolising layer and an inner, inert, watery layer. It may be interesting to speculate as to whether this may have some bearing on the theory of formation of vacuoles.

The author is indebted to Mr. H. D. Landahl for checking the calculations.

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DISCRIMINATION BETWEEN TEMPORALLY SEPARATED STIMULI

H. D. LANDAHL
The University of Chicago

A mechanism is discussed which has the property that two temporally separated stimuli presented over a common path may be discriminated as though they had been presented simultaneously over separate paths.

In deriving some properties of a neural mechanism for discrimination (Landahl, 1938), it was necessary to assume a simultaneous presentation of stimuli for discrimination to be possible. It is the purpose here to discuss a mechanism with such properties that two stimuli presented separately in time over a common path may be discriminated as though they had been presented simultaneously over separate but identical paths. The discriminatory response is made some time after the second stimulus is presented, but no response is made to the first stimulus alone. Such a mechanism, as is to be discussed here, is not required, however, by a discriminatory mechanism of the type discussed by A. S. Householder (1940).

Let us then investigate some properties of the mechanism represented in Figure 1. We shall limit our discussion to the case in which

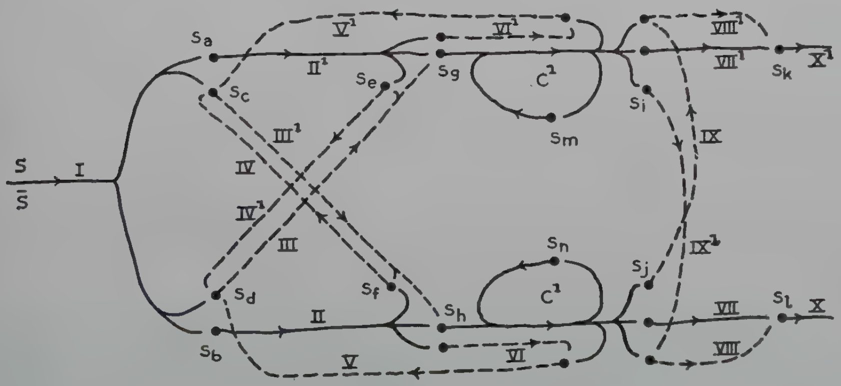

FIGURE 1

the mechanism is symmetric; that is, the members of any pair, as II and II^1, are identical. The following notation is adopted (Rashevsky, 1938, ch. XXII). The symbol ε denotes the excitatory factor produced at the efferent end of an excitatory fiber (solid line). The symbol j denotes the inhibitory factor produced at the efferent end of an inhibitory fiber (broken line). We are then assuming the fibers to be of the simple type so that each fiber produces either ε or j, but not both. Neither ε nor j can be negative. The intensity of excitation E in a fiber excited by a stimulus S or by a net excitation $\varepsilon—j$ is assumed to be given by an expression

$$E = \beta(S - h)$$

or (1)

$$E = \beta(\varepsilon - j - h),$$

where β is a constant of proportionality and h is the threshold of the fiber. Unless $S > h$ we have $E = 0$. Arabic subscripts correspond with the Roman numerals. Where the Roman numeral denoting a fiber has a superscript, the symbols ε or j and E associated with the fiber are primed; because of the assumption of symmetry, the other symbols which are fixed parameters of the fibers need not be primed. The superscript instead of a prime is used on the Roman numerals to avoid confusion with a convention used by Rashevsky (1938).

The development of ε or j at the end of an excitatory fiber or at the end of an inhibitory is given by (Rashevsky, 1938, ch. XXII).

$$\frac{d\varepsilon}{dt} = AE - a\varepsilon \, , \tag{2}$$

$$\frac{dj}{dt} = BE - bj \, , \tag{3}$$

where A and a are parameters of an excitatory fiber and B and b are corresponding parameters of an inhibitory fiber. In Figure 1 the afferent end of each fiber at a synapse is represented by a dot, and the direction of transmission at any synapse is readily determined. Arrows are also used to indicate the direction of transmission of nerve impulses in the fibers.

We now introduce the following simplifying conditions to hold throughout the discussion

$$A_2 = B_3 \, , \qquad a_2 = b_3 \, , \qquad h_2 = h_3 \, . \tag{4}$$

Let us assume that initially all ε's and j's are zero. Then let a stimulus $S > h$ be presented at the afferent end of fiber I. The rate of development of ε'_1 and ε_1 at s_a and s_b will then be given by an equation of the form of (2). Introducing (1) with the appropriate subscripts for fiber I and integrating the result, ε'_1 and ε_1 are obtained as functions of time, $\varepsilon'_1(t) = \varepsilon_1(t)$. We shall not need this expression but only its stationary value given by

$$\varepsilon'_1 = \varepsilon_1 = \frac{A_1 \beta_1}{a_1} (S - h_1) . \tag{5}$$

Since fibers II^1, II, III^1 and III are equally excited at all times and since $j_4 = j'_4 = j_5 = j'_5 = 0$ initially, we have $\varepsilon'_1(t) = \varepsilon_2(t) = j'_3(t) = j_3(t)$ because of conditions (4). Hence at s_e and s_f as well as at s_g and s_h the net excitation $(\varepsilon - j)$ is in each case zero, $\varepsilon_2 - j'_3 = \varepsilon'_2 - j_3 = 0$. Under these conditions no excitation will be produced beyond s_g and s_h . Now let the stationary state be reached to any degree of approximation so that after a time $t = \tau_1$ and until some external change is introduced, say at τ_2 , we have

$$\begin{gathered}\varepsilon'_2 = \varepsilon_2 = j'_3 = j_3 = \frac{A_2 \beta_2}{a_2} (\varepsilon_1 - h_2) = \\ \frac{A_2 \beta_2}{a_2} \left[\frac{A_1 \beta_1}{a_1} (S - h_1) - h_2 \right] ; \\ \tau_2 \geq t \geq \tau_1 .\end{gathered} \tag{6}$$

We assume that $\varepsilon_1 > h$ since otherwise $\varepsilon'_2 = \varepsilon_2 = j'_3 = 0$ and further discussion is meaningless. Likewise in subsequent equations where similar situations arise, similar assumptions are implied.

Suppose now at a time $\tau_2 \geq \tau_1$ an amount of inhibitory factor $\Delta j > 0$ is produced at synapse s_d due to some outside influence. The nature of this change will be discussed later. Since the net excitation acting on fiber III is $\varepsilon_1 - \Delta j$ instead of ε_1 , the inhibitory factor j_3 is decreased so that $\varepsilon'_2 - j_3$ is increased. Since it was initially zero, it becomes positive. Let

$$\frac{A_2 \beta_2}{a_2} \Delta j > h_4 \tag{7}$$

so that at a finite time $\tau_3 > \tau_2 \geqslant \tau_1$ the increase in the net excitation, $\varepsilon'_2 - j_3$, at synapse s_e exceeds h_4 , or since $\varepsilon'_2 = \varepsilon_2$,

$$\varepsilon_2 - j_3 > h_4 \; ; \tau_5 > t \geq \tau_3 , \tag{8}$$

where τ_5 is the time at which some change is again made, being the time at which S is to be withdrawn. The quantity $\tau_3 - \tau_2$ may be obtained as a function of Δj but we shall not need the value. Now, after the time τ_3, $j'_4 > 0$ because of (8) and thereafter j_3 and j'_4 are interrelated. In the mean time it is clear from the mechanism that ε'_2, ε_2 and j'_3 remain at their value given by (6), or

$$\begin{gathered}\varepsilon'_2 = \varepsilon_2 = j'_3 = \frac{A_2\,\beta_2}{a_2}\left[\frac{A_1\,\beta_1}{a_1}\,(S - h_1) - h_2\right], \\ j_4 = 0\,; \quad \tau_5 > t > \tau_3\,.\end{gathered} \tag{9}$$

Since $\varepsilon_2 - j'_3 = 0$, j_4 remains zero.

For the development of j_3 and j'_4 in the interval $\tau_5 \geq t \geq \tau_3$ we have the equations, (cf. Rashevsky, 1938, ch. XXIV, and Householder, 1938)

$$\frac{dj_3}{dt} = A_2\,\beta_2\,(\varepsilon_1 - h_2 - \Delta\,j) - A_2\,\beta_2\,j'_4 - a_2\,j_3\,, \tag{10}$$

$$\frac{dj'_4}{dt} = B_4\,\beta_4\,(\varepsilon_2 - h_4) - B_4\,\beta_4\,j_3 - b_4\,j'_4\,, \tag{11}$$

by substituting, in each case, equation (1) into (3), using the appropriate subscripts, and introducing (4) and (9). The relations (10) and (11) hold only if the respective E's are positive, or rewriting, we have the conditions

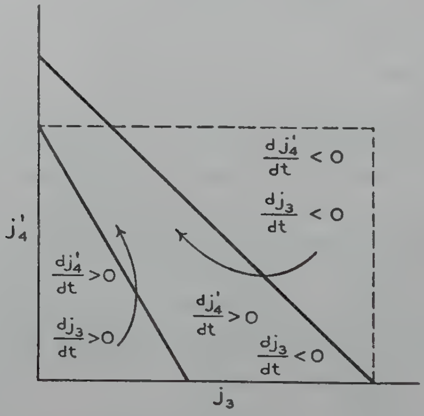

FIGURE 2

$$j'_4 \leq \varepsilon_1 - h_2 - \Delta\,j\,, \text{ or else } j_3 = 0\,, \tag{12}$$

$$j_3 \leq \varepsilon_2 - h_4\,, \text{ or else } j'_4 = 0\,. \tag{13}$$

At the time $t = \tau_3$, $j'_4 = 0$ so that condition (12) is satisfied. Because of (8), condition (13) is also satisfied initially.

We now wish to determine sufficient conditions which insure that after a sufficient lapse of time (but still within the interval $\imath_5 \geq t \geq \imath_3$), j_3 has a value zero while j'_4 has some positive value. Setting the derivatives in equations (10) and (11) equal to zero and solving for j'_4 in each case, we determine two straight lines: (Figure 2)

$$L_3 : \qquad j'_4 = \varepsilon_1 - h_2 - \Delta j - \frac{a_2}{A_2 \beta_2} j_3 , \tag{14}$$

$$L'_4 : \qquad j'_4 = \frac{B_4 \beta_4}{b_4} (\varepsilon_2 - h_4) - \frac{B_4 \beta_4}{b_4} j_3 ; \tag{15}$$

on which respectively $dj_3/dt = 0$ and $dj'_4/dt = 0$.

Now let

$$\varepsilon_1 - h_2 - \Delta j > 0 . \tag{16}$$

Then because (8) implies that $\varepsilon_2 > h_4$, the lines L_3 and L'_4 have positive intercepts and negative slopes. If L'_4 has a larger intercept on the j_4-axis than L_3 and if L'_4 has a larger intercept on the j_3-axis than L_3, that is, if

$$\varepsilon_1 - h_2 - \Delta j < \frac{B_4 \beta_4}{b_4} (\varepsilon_2 - h_4) , \tag{17}$$

$$\varepsilon_1 - h_2 - \Delta j < \frac{a_2}{A_2 \beta_2} (\varepsilon_2 - h_4) , \tag{18}$$

which may be written, because of (9),

$$\Delta j > \left(1 - \frac{A_2 \beta_2 B_4 \beta_4}{a_2 b_4}\right) (\varepsilon_1 - h_2) + \frac{B_4 \beta_4 h_4}{b_4} , \tag{19}$$

$$\Delta j > \frac{a_2 h_4}{A_2 \beta_2} , \tag{20}$$

then L'_4 and L_3 will not intersect in the positive quadrant. The positive quadrant (j_3 and j'_4 must be positive to be meaningful) is then divided into three regions; *I*, the region below the line L_3 ; *II*, the region between L_3 and L'_4 ; and III, the region above L'_4 (Figure 2). The points on the axes are included in the respective regions but not the points on the lines L_3 and L'_4 which separate the region.

In region *I*,

$$\frac{dj'_4}{dt} > 0 \text{ and } \frac{dj_3}{dt} > 0 ;$$

in region *II*

$$\frac{dj'_4}{dt} > 0 \text{ and } \frac{dj_3}{dt} < 0 ;$$

and in region *III*

$$\frac{dj'_4}{dt} < 0 \text{ and } \frac{dj_3}{dt} < 0 \,.$$

However these inequalities are subject to conditions (12) and (13). These conditions are satisfied in the region bounded by the broken lines of Figure 2. A point to the right of the vertical broken line fails to satisfy condition (13) and hence j'_4 must decrease to zero if somehow j_3 were maintained. But $dj_3/dt = 0$ and hence j_3 decreases until the configuration point enters the rectangular region required by (12) and (13). A point above the horizontal broken line fails to satisfy condition (12) and hence j_3 must decrease to zero. However if $j_3 = 0$, from (11) we still have $dj'_4/dt > 0$, and the configuration point moves to the stable value given by the larger ordinate intercept, L'_4 with the j'_4-axis. Now the only possible stable equilibrium configurations are the four intercepts, since clearly the point (0, 0) represents an unstable equilibrium, and since from the nature of equations (10) and (11) and since $j_3 \geq 0$ and $j_4 \geq 0$, neither j_3 nor j'_4 can increase without bound. From an inspection of Figure 2 it is clear that the intercepts of L_3 and L'_4 on the j_3-axis are unstable points of equilibrium as is also the intercept of L_3 on the j'_4-axis. There remains the intercept of L'_4 on j'_4. Because of condition (12) $j_3 = 0$ and remains so. From equation (11) with $j_3 = 0$, it is clear that a displacement of j'_4 away from the intercept value gives such a sign to dj'_4/dt that the initial intercept value tends to be restored. Let this equilibrium be reached to any degree of approximation at the time $t = \tau_4$, $\tau_4 > \tau_3$; we may then write

$$j'_4 = \frac{B_4 \beta_4}{b_4} (\varepsilon_2 - h_4) \,,$$

$$j_3 = 0 \,, \text{ for } \tau_5 \geq t \geq \tau_4 \,. \tag{21}$$

In the above argument we have imposed four conditions: (4), (7), (16), and (19), since (7) implies (8) and is identical to (20). Now condition (4), though a very restricting condition, simply relates certain parameters in two pairs of fibers. Conditions (7) and (19) impose a minimum value for Δj while condition (16) imposes a maximum value for Δj, a value which increases with S. If the right hand member of the inequality (20) is greater than the right hand member of (19) then (7), (16) and (19) may be written

$$\varepsilon_1 - h_2 > \Delta j > \frac{a_2 h_4}{A_2 \beta_2} \,, \tag{22}$$

and hence, since ε_1 is a monotonically increasing function of S, (22) imposes a minimum for the value of S greater than the threshold h_1, or because of (5)

$$S > h_1 + \frac{a_1 h_2}{A_1 \beta_1} + \frac{a_1 a_2 h_4}{A_1 A_2 \beta_1 \beta_2} \cdot \tag{23}$$

But if the right hand member of inequality (20) is less than that of (19), then (7), (16) and (19) may be written, instead of (22), as

$$\varepsilon_1 - h_2 > \Delta j > \left(1 - \frac{A_2 \beta_2 B_4 \beta_4}{a_2 b_4}\right)(\varepsilon_1 - h_2) + \frac{B_4 \beta_4 h_4}{b_4}, \tag{24}$$

or since the first member must exceed the last member, we again have, after simplifying,

$$S > h_1 + \frac{a_1 h_2}{A_1 \beta_1} + \frac{a_1 a_2 h_4}{A_1 A_2 \beta_1 \beta_2} \cdot \tag{25}$$

Hence if we assume conditions (4) and (25), then if Δj lies within the range given by (22) or (24), and such a range exists, the resulting stable values of j_3 and j'_4 are given by (21).

Now let the stimulus S be maintained after equilibrium has been reached and long enough so that the set of self-exciting neural circuits, represented in the figure by C^1, which have sufficiently low thresholds, are brought into a state of permanent excitation (Landahl and Householder 1939, Rashevsky 1938, ch. XXIV). For simplicity, let us assume that the parameters are such that for any circuit the threshold value for permanent excitation to be maintained is approximately equal to the threshold h_C of the fiber. Also we assume that all the parameters of the circuits represented by C^1 are the same except the thresholds, which are distributed according to some distribution function. Now all those circuits of C^1 are excited for which $h_C < \varepsilon_2(S)$. In the meantime, no fibers of C are excited. If we assume that the distribution of thresholds h_C is such that in each range Δh_C there are an equal number of circuits, then, as the circuits are otherwise identical, the net excitation ε'_C acting on the afferent ends of fibers VII^1, $VIII^1$ and IX^1 is proportional to the number of circuits excited or

$$\varepsilon'_C = D\, \varepsilon_2(S), \tag{26}$$

where D is a constant.

Now any time after the circuits have become self-exciting the stimulus S, as well as Δj, may be withdrawn. We then consider the effect beyond C' at $t > \tau_5$. If we let $h_8 \leqslant h_7$, $B_8 \beta_8 \geqslant A_7 \beta_7$, and

$B_8\beta_8/b_8 \geqslant A_7\beta_7/a_7$, then at all times $j_8 \geqslant \varepsilon_7$ so that fiber X^1 is not excited. Let the stationary state be reached to any degree of accuracy after $t > \tau_6 > \tau_5$, so that we have the following relations,

$$\varepsilon'_7 = \frac{A_7\,\beta_7}{a_7}\,(\varepsilon'_C - h_7) \tag{27}$$

$$j'_8 = \frac{B_8\,\beta_8}{b_8}\,(\varepsilon'_C - h_8)\,, \tag{28}$$

$$j'_9 = \frac{B_9\,\beta_9}{b_9}\,(\varepsilon'_C - h_9)\,, \tag{29}$$

$$j'_5 > 0\,, \tag{30}$$

for

$$\tau_7 > t > \tau_6\,,$$

where τ_7 is the time of a new external change, being the time of presentation of a new stimulus $\bar{S}$. The value of j'_5 in (30) is not given for reasons given in the next paragraph. Now in the interval $\tau_7 > t > \tau_6$, all ε's and j's are zero except ε'_C, ε'_7, j'_8, j'_9, and j'_5. But after $\bar{S}$ is presented, $t > \tau_7$, $\bar{\varepsilon}_1$ and $\bar{\varepsilon}'_1$ develop to their stable values given by

$$\bar{\varepsilon}_1 = \bar{\varepsilon}'_1 = \frac{A_1\,\beta_1}{a_1}\,(\bar{S} - h_1)\,. \tag{31}$$

Similarly, $\bar{\varepsilon}_2$, $\bar{\varepsilon}'_2$ and $\bar{j}_3$ develop to their stable value given by (since $\Delta j = 0$)

$$\bar{\varepsilon}_2 = \bar{\varepsilon}'_2 = \bar{j}_3 = \frac{A_2\,\beta_2}{a_2}\left[\frac{A_1\,\beta_1}{a_1}\,(\bar{S} - h_1) - h_2\right], \tag{32}$$

with $\bar{\varepsilon}'_2 - \bar{j}_3 = 0$ at s_e and s_g throughout the development. But j'_3 cannot develop at the same time, because of j'_5. Hence the net excitation at s_f is positive and fiber IV will be excited if j'_5 is sufficiently large. We then have j'_3 and j_4 interrelated, during the stationary state of ε'_2 etc., in the same manner as j_3 and j'_4 were in the interval $\tau_5 > t > \tau_3$ but with j'_5 playing the role of Δj. If j'_5 satisfies the conditions satisfied by Δj, then j'_3 tends to its stable value, zero. Hence, at time τ_8, after sufficient time has lapsed, the circuits C, whose thresholds are less than $\bar{\varepsilon}_2$, are excited, and we have

$$\bar{\varepsilon}_C = D\,\bar{\varepsilon}_2(\bar{S}),\ \text{for}\ t > \tau_8\,. \tag{33}$$

Any time after τ_8, stimulus S may be withdrawn.

If fibers V and V^1 were such that for them we may use equation (1), the above argument is complicated and not strictly valid since j'_5 is a function of S. In order to avoid such a difficulty let us assume that these fibers are such that $E_5(S)$ is given by a simple exponential [Rashevsky, 1938, ch XXII, eq. (5)] and the parameters are such that for the S and $\bar{S}$ used, j_5 is greater than 0 and essentially independent of S.

Consider now the situation after τ_9, when $\bar{\varepsilon}_C$ has acted sufficiently long for $\bar{\varepsilon}_7$, $\bar{j}_8$ and $\bar{j}_9$ to reach their stable values with $\bar{\varepsilon}_7$ and $\bar{j}_9$ being given by

$$\bar{\varepsilon}_7 = \frac{A_7\,\beta_7}{a_7}\,(\bar{\varepsilon}_C - h_7)\,, \tag{34}$$

$$\bar{j}_9 = \frac{B_9\,\beta_9}{b_9}\,(\bar{\varepsilon}_C - h_9)\,, \tag{35}$$

$$t > \tau_9\,.$$

Now ε'_7 and j'_9 are unchanged and hence also

$$\varepsilon'_7 = \frac{A_7\,\beta_7}{a_7}\,(\varepsilon'_C - h_7)\,, \tag{36}$$

$$j'_9 = \frac{B_9\,\beta_9}{b_9}\,(\varepsilon'_C - h_9)\,, \tag{37}$$

$$t > \tau_9\,.$$

However j'_8 is no longer given by (28). If $\varepsilon'_C - \bar{j}_9 \leq h_8$ that is if

$$\bar{\varepsilon}_C - \frac{b_9}{B_9\,\beta_9}\,\varepsilon'_C \geq h_9 - \frac{b_9\,h_8}{B_9\,\beta_9} \tag{38}$$

$$j'_8 = 0\,, \quad t > \tau_9\,. \tag{39}$$

Since $S \backsim \bar{S}$ in a discrimination situation, it is sufficient, for (38) to hold, that $B_9\beta_9/b_9 > 1$ if $h_9 < b_9h_8/B_9\beta_9$. But then also, at least if $B_9\beta_9/b_9 >> 1$,

$$\varepsilon'_C - \frac{b_9}{B_9\,\beta_9}\,\bar{\varepsilon}_C > h_9 - \frac{b_9\,h_8}{B_9\,\beta_9} \tag{40}$$

and hence

$$\bar{\varepsilon}_C - j'_9 < h_8\,,$$

and

$$j_8 = 0\,, \quad t > \tau_9\,. \tag{41}$$

Therefore at $t = \tau_9$, fibers X^1 and X are respectively excited by the quantities $\varepsilon'_7(S)$ and $\bar{\varepsilon}_7(\bar{S})$, of equations (36) and (34). However, during the interval $\tau_9 > t > \tau_8$ fibers X^1 and X are not necessarily excited equally. We may resolve this difficulty in two ways. We may assume that $\bar{\varepsilon}_7$ and j'_8 develop much more slowly than $\bar{j}_9$ or $\bar{\varepsilon}_C$ so that $\bar{\varepsilon}_C$ and j'_g may be assumed suddenly established at $t = \tau_8$. Then if the parameters of *VII* and *VIII* are related by conditions analogous to (4), the development of the net excitation at s_k and s_l will be simultaneous. On the other hand we may disregard any temporary differences at s_k and s_l and assume that the next higher order fibers, X^1 and X are of such a type that a_{10} is much larger than a_7, b_8, *or* b_9 and hence the development at the net excitations at s_k and s_l are essentially simultaneous so far as X^1 and X are concerned.

Suppose that X^1 and X lead to a discriminatory center of the type previously described (Landahl, 1938). The value

$$\varepsilon'_7 - \bar{\varepsilon}_7 = \frac{A_7\,\beta_7}{a_7}(\varepsilon'_C - \bar{\varepsilon}_C) = \frac{A_7\,\beta_7\,A_2\,\beta_2\,A_1\,\beta_1\,D}{a_7\,a_2\,a_1}(S - \bar{S}) \qquad (42)$$

is analogous to $\varepsilon_1 - \varepsilon_2$ of equations (5) and (9) of the previous development. This latter value was proportional to the logarithm of the ratio of the two simultaneously presented stimuli, but since they are necessarily very nearly equal, the logarithm of the ratio is approximately proportional to the difference. If instead of the first equation of (1) we had used, as in the previous case, a logarithmic relation between E and S, then in place of (42) we would have $\varepsilon'_7 - \bar{\varepsilon}_7$ proportional to $\log(S/\bar{S})$.

Under the conditions imposed, the mechanism of figure 1 has the property desired. As far as fibers X^1 and X are concerned, or any responses that they may lead to, it makes no difference in the response whether two stimuli S and $\bar{S}$ are presented in succession at fiber I, each being sufficiently large and being presented for a sufficiently long time, or two other stimuli $\varepsilon'_7(S)$ and $\bar{\varepsilon}_7(\bar{S})$, which are linear functions of S and $\bar{S}$, are presented simultaneously at s_k and s_l to X^1 and X directly.

In order that the mechanism of figure 1 may discriminate repeatedly between pairs of stimuli, suppose also that the response to either S or $\bar{S}$ leads to an inhibition at synapses s_m and s_n sufficiently large, and for a sufficiently long duration so that ε'_C and $\bar{\varepsilon}_C$ subside to zero. Then all ε and j not already zero will decrease to zero. A second pair of stimuli may then be presented and the process repeated.

A large number of conditions have been imposed on the parameters of the mechanism. Not all have been necessary. To eliminate those which are not necessary would require a more detailed analysis augmented by a comparison with experimental data. Such an assumption as perfect symmetry of the mechanism is certainly not necessary since temporal and spatial biases are generally present. However, by appropriate technique, they may often be made neglible if desired. Also it was assumed that the distribution curve of h_C was a constant. Now almost any distribution function having one maximum which is not too narrow could have been assumed without changing the results essentially. Also it was assumed that the threshold for permanent excitation for each circuit of C' and C was approximately equal to the threshold of the fiber. Such would generally not be the case. If not, the second stimulus would be favored so far as this one factor is concerned.

It was assumed that Δj was somehow applied at synapse s_d. Without much change in the results, Δj may have been applied at s_d, or at s_a or s_b, though in the latter cases, the responses would have been reversed. But this would be satisfactory. Instead of $\Delta j > 0$, a quantity $\Delta \varepsilon$ at s_a, s_b, s_c, or s_d could have been used. One might have assumed a slight asymmetry in the mechanism such that $h'_2 \neq h_2$ or $h'_3 \neq h_3$. We consider Δj (or its equivalent) as some random change and this change must exceed a certain value before the initial system, in which $\varepsilon'_2 = j_3$, passes over into a much more stable system in which ε'_2 is unchanged and in which $j_3 = 0$. Thus Δj measures the half width of the stability of the initial configuration $\varepsilon_2 = \varepsilon'_2 = j_3 = j'_3$ of equation (6).

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CONVECTIVE DIFFUSION IN PARALLEL FLOW FIELDS

GALE YOUNG
The University of Chicago

Laminar motion of two viscous incompressible fluids through each other is treated for two cases: flow along the axis of a circular cylinder, and flow between parallel flat plates. Motion of either fluid entails that of the other. Regarding one fluid as a solvent, the other as a solute, and supposing the system to have ends impermeable to the former, it is found that the solvent streams with the solute down the center of the system, to return in the opposite direction out nearer the walls. Thus diffusion of a dissolved substance through a region in which the solvent is confined produces continual streaming in the latter.

I

Consider two fluids moving through each other under the following conditions: (I) The fluids have constant densities. (II) The motion is slow enough that inertial forces may be neglected. (III) The steady state has been sensibly reached so that time variation terms may be neglected. (IV) Long range forces are negligible, and the short range forces between the fluids may be represented by a drag force proportional to their relative velocity.

Letting P denote the mean pressure of a fluid, Η its coefficient of viscosity, and (U, V, W) its velocity, with corresponding small letters for the other fluid, the equations of motion are (Young, 1938)

$$\begin{aligned}
P_x &= B(u - U) + \mathrm{H}\nabla^2 U \\
P_y &= B(v - V) + \mathrm{H}\nabla^2 V \\
P_z &= B(w - W) + \mathrm{H}\nabla^2 W \\
p_x &= B(U - u) + \eta\nabla^2 u \\
p_y &= B(V - v) + \eta\nabla^2 v \\
p_z &= B(W - w) + \eta\nabla^2 w \qquad (1) \\
\frac{\partial U}{\partial x} &+ \frac{\partial V}{\partial y} + \frac{\partial W}{\partial z} = 0 \\
\frac{\partial u}{\partial x} &+ \frac{\partial v}{\partial y} + \frac{\partial w}{\partial z} = 0 .
\end{aligned}$$

Herein $P_x = \partial P/\partial x$ etc., and B is a constant. Differentiating and adding gives

$$\nabla^2 P = \nabla^2 p = 0\,, \tag{2}$$

so that the pressures are harmonic functions. By addition in (1)

$$P_x + p_x = \mathrm{H}\nabla^2 U + \eta\nabla^2 u \tag{3}$$

and similar equations; while by differentiation arise such equations as

$$\nabla^2 U = \nabla^2 u - \frac{\eta}{B}\nabla^4 u\,, \tag{4}$$

from which $\nabla^2 p_x = 0$ has been dropped. Substitution of (4) into (3) gives the system of equations

$$\begin{aligned} \nabla^4 u + a\nabla^2 u &= g_x \\ \nabla^4 v + a\nabla^2 v &= g_y \\ \nabla^4 w + a\nabla^2 w &= g_z \\ \frac{\partial u}{\partial x} + \frac{\partial v}{\partial y} + \frac{\partial w}{\partial z} &= 0\,, \end{aligned} \tag{5}$$

where

$$\begin{aligned} a &= -\frac{(\mathrm{H}+\eta)B}{\mathrm{H}\,\eta} \\ g &= -\frac{(P+p)B}{\mathrm{H}\,\eta}\,. \end{aligned} \tag{6}$$

The corresponding solvent velocities are found from (1) to be

$$\begin{aligned} U &= u - \frac{\eta}{B}\nabla^2 u + \frac{p_x}{B} \\ V &= v - \frac{\eta}{B}\nabla^2 v + \frac{p_y}{B} \\ W &= w - \frac{\eta}{B}\nabla^2 w + \frac{p_z}{B}\,, \end{aligned} \tag{7}$$

which may be readily verified to satisfy (1) for any u,v,w satisfying (5). Thus the most general solution of (1) is given by the general solution of (5) supplemented by (7).

In what follows attention will be restricted to systems in which the fluids move only in one direction, in which case the above relations are considerably simplified. If the x axis is taken along the direction of flow, it follows that $v = w = V = W = 0$. From (1) it is then seen that $P_y = P_z = p_y = p_z = 0$, so that the pressures are functions of x only. But (2) then shows that they must be of the form

$$P = Kx + M \qquad (8)$$
$$p = kx + m .$$

The system (5) then reduces to

$$\nabla^4 u + a\nabla^2 u = b \qquad (9)$$
$$\frac{\partial u}{\partial x} = 0 ,$$

where

$$b = -\frac{(K+k)B}{\mathrm{H}\,\eta} ; \qquad (10)$$

while (7) becomes

$$U = u - \frac{\eta}{B}\nabla^2 u + \frac{k}{B} . \qquad (11)$$

It may be noted that restriction to one-dimensional or laminar flow renders the initial assumption (II) superfluous. For the terms thereby neglected in (1) are of the form

$$u\frac{\partial u}{\partial x} + v\frac{\partial u}{\partial y} + w\frac{\partial u}{\partial z} \qquad (12)$$

and vanish identically because of (9) and the condition $v = w = 0$; the same is true, of course, for the other fluid as well. This would not be true for a compressible fluid, since it would experience finite accelerations as its pressure changes along the path of motion.

II

Consider first the case where the flow is along the axis of a circular cylinder, assuming symmetry about that axis. Then $u = u(r)$ and

$$\nabla^2 u = \frac{d^2u}{dr^2} + \frac{1}{r}\frac{du}{dr} = \frac{1}{r}\frac{d}{dr}\left(r\frac{du}{dr}\right) ; \qquad (13)$$

and similarly for U. Equation (9) then becomes

$$\frac{d}{dr}\left(r\frac{d\nabla^2 u}{dr}\right) + a\frac{d}{dr}\left(r\frac{du}{dr}\right) = br . \qquad (14)$$

The integral is apparent and upon division by r is

$$\frac{d}{dr}\nabla^2 u + a\frac{du}{dr} = \frac{b}{2}r + \frac{A_1}{r}, \tag{15}$$

where A_1 is an integration constant which must be equal to zero to keep u regular at $r = 0$. A second integration gives

$$\nabla^2 u + au = \frac{b}{4}r^2 + A_2 , \tag{16}$$

or

$$\frac{d^2u}{dr^2} + \frac{1}{r}\frac{du}{dr} + au = \frac{b}{4}r^2 + A_2 . \tag{17}$$

The homogenous equation obtained by setting the right side equal to zero is a zero order Bessel equation with solution

$$A_3 J_0(\sqrt{a}\, r) + A_4 Y_0(\sqrt{a}\, r), \tag{18}$$

where J_0 is a Bessel function of the first kind and Y_0 is a Neuman Bessel function of the second kind. Since $Y_0(0) = \infty$, A_4 must be equal to zero.

It may be verified by substitution that

$$\frac{b}{4a}r^2 + \frac{A_2}{a} - \frac{b}{a^2} \tag{19}$$

is a special solution of (17); hence the general solution is

$$u = A_3 J_0(\sqrt{a}\, r) + \frac{b}{4a}r^2 + A_5 , \tag{20}$$

where

$$A_5 = \frac{A_2}{a} - \frac{b}{a^2} . \tag{21}$$

From (11), along with (16), (20), and (21) it is found that

$$U = (1 + \frac{a\eta}{B}) A_3 J_0(\sqrt{a}\, r) + \frac{b}{4a}r^2 + A_5 + \frac{k}{B} - \frac{\eta b}{aB} . \tag{22}$$

Both fluids have zero velocity at the surface of the cylinder $r = R$. Writing $u = U = 0$ for $r = R$ gives two equations for determining the constants of integration. They come out to be

$$A_3 = \frac{\frac{\eta b}{a} - k}{a\eta J_0(\sqrt{a}\,R)}$$

$$A_5 = -\frac{b}{4a}R^2 - \frac{b}{a^2} + \frac{k}{a\eta}\,; \tag{23}$$

and with these values (20) and (22) become

$$u = E\,(r^2 - R^2) + \mathrm{H}\,A\,[CJ_0(\sqrt{a}\,r) - 1]\,,$$

$$U = E\,(r^2 - R^2) - \eta\,A\,[CJ_0(\sqrt{a}\,r) - 1] \tag{24}$$

where

$$E = \frac{K + k}{4(\eta + \mathrm{H})}$$

$$A = \frac{k\mathrm{H} - K\eta}{B\,(\eta + \mathrm{H})^2} \tag{25}$$

$$C = \frac{1}{J_0(\sqrt{a}\,R)}\,.$$

Since a is negative the Bessel functions appearing in the above have imaginary arguments, and hence do not vanish for any value of r except $r = 0$.

The functions r^2 and $J_0(\sqrt{a}\,r)$ are linearly independent; hence the flow rates in (24) can vanish identically only if $E = A = 0$. From (25) it is seen that $E = 0$ requires $K + k = 0$, and then $A = 0$ implies $K = k = 0$. Hence if there is a pressure gradient in *either* fluid then *both* will be in motion. Regarding one fluid as a solvent and the other as a solute, this shows that any diffusion of the solute is accompanied by convection currents in the solvent.

The total flow thru a cross-section of the cylinder is

$$J = 2\pi\int_0^R U\,r\,dr = -\frac{\pi E R^4}{2} - 2\pi\,\eta\,A\left[C\,\frac{J_1(\sqrt{a}\,R)}{\sqrt{a}\,R)} - \frac{1}{2}\right]R^2$$

$$J = 2\pi\int_0^R u\,r\,dr = -\frac{\pi E R^4}{2} + 2\,\pi\,\mathrm{H}\,A\left[C\,\frac{J_1(\sqrt{a}\,R)}{\sqrt{a}\,R)} - \frac{1}{2}\right]R^2\,. \tag{26}$$

Supposing k given, then (26) may be solved for that value of K which makes $J = 0$. Thus if we imagine a system closed at x_1 and x_2 by membranes impervious to the solvent (capital letters) but allowing penetration of the solute (small letters), and if the solute is under different pressures p_1 and p_2 at the two ends, then there will be a net flow of solute thru the system but J will be zero, K being thereby determined. Since the solvent cannot be everywhere at rest it therefore will flow in one direction in some parts of the cross-section and in the opposite direction elsewhere. There will thus be a circuital streaming of the solvent; as will be seen later it flows with the solute down the center of the cylinder and returns in the opposite direction out nearer the walls. It has to turn at the ends and there the flow will not be confined to the x direction, so that the above treatment does not apply. However if the system is sufficiently long the above considerations hold, except near the ends.

Thus we have an example wherein a substance diffusing thru a region in which the solvent is confined sets up continual streaming in the latter.

In typical diffusion problems the constants are such that the above expressions may be considerably simplified. The bracketed expression in (24) is equal to —1 at the center of the cylinder and rises monotonically to zero at the walls. If $\sqrt{-a}\,R$ (which is a dimensionless quantity) is large enough the bracket will be sensibly —1 everywhere except very near the walls where it increases rapidly to zero. Except in this transition layer itself the Bessel function term may be ignored.

For x fairly large $J_1(ix) \cong iJ_0(ix)$, so that the bracket term in the flow rate (26) is approximately

$$\frac{1}{\sqrt{-a}\,R} - \frac{1}{2}\,. \tag{27}$$

Calculation for typical biological cases (Young, 1938) shows that $\sqrt{-a}$ is of the order of 10^6 to 10^8 cm^{-1}, so that if R is say 10^{-4} cm. or more the first term in (27) is negligible compared with the second. Thus, very nearly,

$$\begin{aligned} J &= -\frac{\pi E}{2} R^4 + \pi\,\eta\,AR^2 \\ j &= -\frac{\pi E}{2} R^4 - \pi\,\mathrm{H}AR^2\,. \end{aligned} \tag{28}$$

Setting $J = 0$ for the case of a cylinder closed to the solvent at its ends gives

$$E = \frac{2\eta}{R^2} A\,; \tag{29}$$

and in this case (28) gives

$$j = -\pi(\eta + \mathrm{H}) A R^2 . \tag{30}$$

From (29), (25) and (6)

$$K\left[1 + \frac{8\eta}{\mathrm{H}(-a)R^2}\right] = -k\left[1 - \frac{8}{(-a)R^2}\right], \tag{31}$$

and with $(-a)R^2$ of the order of 10^8 or more as indicated above it is seen that K may be taken as $-k$ in A to give very nearly

$$A = \frac{k}{B(\mathrm{H} + \eta)} . \tag{32}$$

The total solute flow (30) is then approximately

$$j = -\frac{k}{B} \pi R^2 . \tag{33}$$

But (34) is exactly the total rate at which the solute would be transported by simple Fick diffusion in a stationary solvent, so that the solvent streaming has very little effect upon the total solute transport down the cylinder.

For x large $J_0(ix) \cong e^x/\sqrt{2\pi x}$, and in the velocity expressions (24)

$$CJ_0(\sqrt{a}\, r) \simeq \sqrt{\frac{R}{r}}\, e^{-\sqrt{-a}(R-r)} , \tag{34}$$

which for $\sqrt{-a}$ large is entirely negligible except very near the outer wall of the cylinder. Thus everywhere except in the wall layer (24) and (32) give

$$\begin{aligned} U &= \frac{k}{B} \frac{\eta}{\mathrm{H} + \eta} \frac{2r^2 - R^2}{R^2} \\ u &= \frac{k}{B} \frac{2\eta r^2 - (\mathrm{H} + 2\eta)R^2}{(\mathrm{H} + \eta)R^2} = U - \frac{k}{B} . \end{aligned} \tag{35}$$

The term $-\,k/B$ in u is the velocity of simple Fick diffusion in the stationary solvent.

Down the center of the cylinder, out to $r = R/\sqrt{2}$ the solvent flows in the same direction as the solute; outside this central stream the solvent flows back in the opposite direction. The cross-sectional areas of the two streams are equal, and the total flow in either is given by

$$J^* = 2\pi \int_0^{R/\sqrt{2}} rU dr = -\frac{k}{B}\frac{\pi}{4}\frac{\eta}{\mathrm{H}+\eta} R^2 . \tag{36}$$

Dividing by the cross-section area of the stream gives the average velocity in it

$$U^* = -\frac{k}{B}\frac{1}{2}\frac{\eta}{\mathrm{H}+\eta} . \tag{37}$$

From (33) the average solute velocity is

$$u^* = -\frac{k}{B} , \tag{38}$$

so that the ratio of average "streaming" to "diffusion" speed is

$$\frac{U^*}{u^*} = \frac{1}{2}\frac{\eta}{\mathrm{H}+\eta} . \tag{39}$$

From (35) or, more exactly, from (29), (32), and (24), it is seen that the velocities remain finite even when R increases indefinitely.

III

Similar results are obtained for the case of laminar flow between parallel flat plates. Let the y axis be perpendicular to the plates which are at $y = 0$ and $y = L$ respectively, the x axis being along the direction of flow as before, and assume the flow independent of z. Then $u = u(y)$ and (9) becomes

$$\frac{d^4u}{dy^4} + a\frac{d^2u}{dy^2} = b . \tag{40}$$

Writing $Z = \dfrac{d^2u}{dy^2}$ this is

$$\frac{d^2Z}{dy^2} + aZ = b , \tag{41}$$

of which the general solution is

$$Z = \frac{d^2u}{dy^2} = A_1 e^{\sqrt{a}\,y} + A_2 e^{-\sqrt{-a}\,y} + \frac{b}{a} . \tag{42}$$

Integrating twice gives

$$u = -\frac{A_1}{a} e^{\sqrt{-a}\,y} - \frac{A_2}{a} e^{-\sqrt{-a}\,y} + \frac{b}{2a} y^2 + A_3 y + A_4 ; \tag{43}$$

and with (11) and (42)

$$U = -A_1\left(\frac{1}{a} + \frac{\eta}{B}\right) e^{\sqrt{-a}\,y} - A_2\left(\frac{1}{a} + \frac{\eta}{B}\right) e^{-\sqrt{-a}\,y}$$

$$+ \frac{b}{2a} y^2 + A_3 y + A_4 + \frac{k}{B} - \frac{\eta b}{Ba} . \tag{44}$$

The boundary conditions $u = U = 0$ at $y = 0$ and at $y = L$ then yield, denoting $l = \sqrt{-a}\,L$,

$$A_1 = \frac{1 - e^{-l}}{e^l - e^{-l}} \left(\frac{k}{\eta} - \frac{b}{a}\right)$$

$$A_2 = \frac{e^l - 1}{e^l - e^{-l}} \left(\frac{k}{\eta} - \frac{b}{a}\right)$$

$$A_3 = -\frac{bL}{2a} \tag{45}$$

$$A_4 = \frac{1}{a} \left(\frac{k}{\eta} - \frac{b}{a}\right) .$$

Introducing these values into (43) and (44) and making the change of variable

$$Y = y - \frac{L}{2} , \tag{46}$$

so that Y is measured from midway between the plates, there is finally obtained

$$U = F\left(Y^2 - \frac{L^2}{4}\right) - \eta A [G \cosh(\sqrt{-a}Y) - 1]$$

$$u = F\left(Y^2 - \frac{L^2}{4}\right) + \mathrm{H}A [G \cosh(\sqrt{-a}Y) - 1] . \tag{47}$$

Here A is given by (25), while

$$F = 2E$$

$$G = 2 \frac{e^{l/2} - e^{-l/2}}{e^l - e^{-l}} . \tag{48}$$

As in the cylindrical system U or u can vanish identically only if both K and k do, and hence diffusion necessarily produces convection currents in the solvent. The total flows through a cross-section of unit length in the z direction are given by

$$
\begin{aligned}
J &= \int_{-L/2}^{L/2} U dY = -\frac{FL^3}{6} - A\,\eta\left[\frac{2}{\sqrt{-a}}\,G\sinh\frac{l}{2} - L\right] \\
j &= \int_{-L/2}^{L/2} u dY = -\frac{FL^3}{6} + A\mathrm{H}\left[\frac{2}{\sqrt{-a}}\,G\sinh\frac{l}{2} - L\right].
\end{aligned}
\tag{49}
$$

Setting $J = 0$ and thus determining K gives the case of a system closed at its ends (x_1 and x_2) to the solvent, just as before.

For $\sqrt{-a}\,L$ large the bracket in (49) reduces to

$$
2\left(1 - \frac{\sqrt{-a}\,L}{2}\right)/\sqrt{-a}\ , \tag{50}
$$

in which the first term is negligible. Then, very nearly, (49) becomes

$$
\begin{aligned}
J &= -\frac{F}{6}L^3 + \eta\,AL \\
j &= -\frac{F}{6}L^3 - \mathrm{H}AL\ .
\end{aligned}
\tag{51}
$$

Putting $J = 0$ gives

$$
F = \frac{6\,\eta}{L^2}A\ , \tag{52}
$$

or, with (6), (48) and (25),

$$
K = \left[1 + \frac{12}{(-a)L^2}\frac{\eta}{\mathrm{H}}\right] = -k\left[1 - \frac{12}{(-a)L^2}\right]. \tag{53}
$$

For $(-a)L^2$ large, A again reduces to the value given in (32); and then from (51) and (52)

$$
j = -\frac{k}{B}L\ , \tag{54}
$$

which is the simple Fick transport through the stationary solvent.

For l large the quantity G of (48) is approximately $2e^{-l/2}$, and in (47)

$$
G\cosh\left(\sqrt{-a}\,Y\right) = e^{-\sqrt{-a}(L/2-y)}\ ; \tag{55}
$$

which is negligible except near the walls. Except very near the walls the velocities are given by

$$U = \frac{k}{B}\frac{\eta}{\mathrm{H}+\eta}\frac{12Y^2 - L^2}{2L^2}$$

$$u = U - \frac{k}{B}\,. \tag{56}$$

The solvent velocity changes sign at $Y^2 = \frac{1}{12}L^2$, so that the central stream is wider and slower than the returning stream. The total flow in either direction is

$$J^* = 2\int_0^{L/\sqrt{12}} U dY = -\frac{k}{B}\,0.1926\,\frac{\eta}{\mathrm{H}+\eta}L\,; \tag{57}$$

the mean speed in the central stream being

$$U^* = -\frac{k}{B}\frac{1}{3}\frac{\eta}{\mathrm{H}+\eta}\,; \tag{58}$$

and in the outer streams

$$U^* = \frac{k}{B}\,0.457\,\frac{\eta}{\mathrm{H}+\eta}\,. \tag{59}$$

The mean solute velocity is again given by (38) and as before the ratio U^*/u^* is of the order of (39).

As before, the velocities remain everywhere finite even if L becomes infinite.

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LITERATURE

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